MANTA

A randomized Phase II study of Fulvestrant in combination with the dual mTOR inhibitor AZD2014 or Everolimus or Fulvestrant alone in Estrogen receptor-positive advanced or metastatic breast cancer

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Study IMP:	AZD2014 and Everolimus
Chief Investigator:	Professor Peter Schmid, MD PhD Centre for Experimental Cancer Medicine (CECM) Barts Cancer Institute Queen Mary University of London Lower Ground Floor Old Anatomy Building Charterhouse Square London, EC1M 6BQ, UK Tel: 0207 882 8498 Fax: 020 7882 8409 Enquiries: BCI-MANTA@qmul.ac.uk
Sponsor:	Queen Mary University of London Joint Research Management Office (JRMO) QM Innovation Building 5 Walden Street London, E1 2EF, UK Tel: 020 7882 7265 Fax: 020 7882 7276 Email: sponsorsrep@bartshealth.nhs.uk
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STUDY CONTACTS

Sponsor:

Queen Mary University of London
Representative of Sponsor: Dr Sally Burtles
Director of Research Services and Business Development
Joint Research Management Office (JRMO)
QM Innovation Building
5 Walden Street
London, E1 2EF, UK

Tel: +44 (0) 20 7882 7265 Fax: +44 (0) 20 7882 7276
Email: sponsorsrep@bartshealth.nhs.uk

Chief Investigator:

Professor Peter Schmid
Centre for Experimental Cancer Medicine (CECM),
Barts Cancer Institute, Queen Mary University of London
Lower Ground Floor, Old Anatomy Building
Charterhouse Square, London, EC1M 6BQ, UK

Tel: +44 (0) 20 7882 8498 Fax: +44 (0) 20 7882 8409
Email: BCI-MANTA@qmul.ac.uk

Lead, PRO Analysis:

Professor Lesley Fallowfield
Sussex Health Outcomes Research & Education in Cancer (SHORE-C),
Brighton & Sussex Medical School, University of Sussex,
Brighton BN1 9RX, UK

Trial Development Group:

Peter Schmid, Rob Coleman, Alistair Ring, Gianfilippo Bertelli, Alastair Thompson, Lesley Fallowfield, Sacha Howell, Shah-Jalal Sarker, Thomas Powles and Rebecca Roylance

Study Statistician:

Dr Shah-Jalal Sarker
Centre for Experimental Cancer Medicine
Barts Cancer Institute - a Cancer Research UK Centre of Excellence
Queen Mary University of London
Old Anatomy Building, Charterhouse Square, London EC1M 6BQ

Tel: +44 (0) 20 7882 8495 Fax: +44 (0) 20 7882 8409
Email: s.sarker@qmul.ac.uk

Trial Coordination:

MANTA Trial Coordinator
Centre for Experimental Cancer Medicine
Barts Cancer Institute - a Cancer Research UK Centre of Excellence
Queen Mary University of London
Old Anatomy Building, Charterhouse Square, London EC1M 6BQ

Tel: +44 (0) 20 7882 8503 Fax: +44 (0) 20 7882 8409
Email: BCI-MANTA@qmul.ac.uk

IMP Liaison:

Cheryl Lawrence
Senior Research Pharmacist
Centre for Experimental Cancer Medicine
Barts Cancer Institute - a Cancer Research UK Centre of Excellence
Queen Mary University of London
Old Anatomy Building, Charterhouse Square, London EC1M 6BQ

Tel: +44 (0) 20 7882 8492 Fax: +44 (0) 20 7882 8409
Email: c.lawrence@qmul.ac.uk

Barts and the London Queen Mary School of Medicine and Dentistry Tissue Bank (HTA Licensing Number: 12199):

MANTA Tissue Collection Officer
Centre for Molecular Oncology
Barts Cancer Institute
Queen Mary University of London
John Vane Science Centre
Charterhouse Square
London, EC1M 6BQ

Email: cecmtissuecollection@qmul.ac.uk

PROTOCOL SIGNATURE PAGE

Signature of the Chief Investigator:
The clinical study as detailed within this research protocol (Global Version 5, Dated 2nd March 2016), and any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

Chief Investigator Name:Prof. Peter Schmid

Signature and Date: _____ __ __ / __ __ __ / __ __ __ __

Signature of the Statistician:
The clinical study as detailed within this research protocol (Global Version 5, Dated 2nd March 2016) or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996), Principles of ICH E6-GCP, ICH E9 - Statistical principles for Clinical Trials, ICH E10 - Choice of Control Groups and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

Study Statistician Name:Dr. Shah-Jalal Sarker

Signature and Date: _____ __ __ / __ __ __ / __ __ __ __

Signature of the Principal Investigator:
The clinical study as detailed within this research protocol (Global Version 5, Dated 2nd March 2016), and any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

Principal Investigator Name: _____

Principal Investigator Site: _____

Signature and Date: _____ __ __ / __ __ __ / __ __ __ __

PROTOCOL SUMMARY

Title	**MANTA - A randomized Phase II study of Fulvestrant in combination with either the dual mTOR inhibitor AZD2014 or Everolimus or Fulvestrant alone in Estrogen receptor-positive advanced or metastatic breast cancer**
Sponsor	Queen Mary University of London
Primary Objective	• Estimate the clinical benefit of fulvestrant + AZD2014 (continuous daily schedule) relative to fulvestrant alone, as measured by investigator-assessed progression-free survival (PFS)
Secondary Objectives	• Estimate the clinical benefit of fulvestrant + AZD2014 (continuous daily schedule) relative to fulvestrant + everolimus, as measured by investigator-assessed PFS • Estimate the clinical benefit of fulvestrant + AZD2014 (intermittent schedule) relative to fulvestrant + everolimus or fulvestrant alone, as measured by investigator-assessed PFS • Estimate the clinical benefit of fulvestrant + AZD2014 (continuous daily schedule) relative to fulvestrant + AZD2014 (intermittent schedule), as measured by investigator-assessed PFS • Estimate the clinical benefit of fulvestrant + AZD2014 relative to fulvestrant + everolimus or fulvestrant alone, as measured by PFS as assessed by an independent review facility [IRF] • Assess the clinical activity, as measured by response rate (RECIST 1.1), change in tumour size at 16 weeks, clinical benefit rate, duration of clinical benefit and duration of response, of fulvestrant + AZD2014 relative to fulvestrant + everolimus or fulvestrant alone • Establish the safety and tolerability of fulvestrant + AZD2014 relative to fulvestrant + everolimus or fulvestrant alone • Establish the safety of the intermittent schedule of AZD2014 relative to the continuous daily schedule of AZD2014 • Estimate the overall survival benefit of fulvestrant + AZD2014 relative to fulvestrant + everolimus or fulvestrant alone • Investigate the effects of fulvestrant +/- AZD2014 or everolimus on bone-turnover biomarkers • Compare the differences in patient reported outcomes as measured by the Functional Assessment of Cancer Therapy-General (FACT-G) scale together with the Breast-Anti-A and Endocrine Symptom (FACTAnti-A-ES) subscales.[1] • Investigate the pharmacokinetics of AZD2014 in breast cancer patients co-administered with fulvestrant • Determine the minimum plasma concentration at steady state in breast cancer patients of fulvestrant alone and when administered in combination with AZD2014 or everolimus
Patient population	Patients with ER-positive and HER2-negative advanced or metastatic breast cancer, whose disease relapsed during treatment with (or within 12 months after discontinuation of) an aromatase inhibitor (AI) in the adjuvant setting or progressed during treatment with an AI in the metastatic setting.
Study design and methodology	This is an open-label, multicentre, 4-arm randomised phase II trial of fulvestrant + AZD2014 in a continuous daily schedule and fulvestrant + AZD2014 in an intermittent schedule (2 days on, 5 days off) versus fulvestrant + everolimus versus fulvestrant alone in patients with ER-positive, HER2-negative advanced or metastatic breast cancer, whose disease relapsed during treatment with (or within 12 months after discontinuation of) an AI in the adjuvant setting or progressed during treatment with an AI in the metastatic setting. The original study was designed as a 3-arm phase II trial in the same patient population, randomising patients (1:2:1) to Fulvestrant, Fulvestrant + AZD2014 or Fulvestrant + everolimus, but was amended to incorporate a 4th arm in which AZD2014 will be given at an intermittent schedule (2 days on, 5 days off).

[1] Not all patients will contribute to this endpoint. Contribution will be dependent on the availability of the relevant questionnaire in the local language. Refer to section 8.1.3

	Patients will be randomised (2:3:3:2) to one of the four treatment arms: • Fulvestrant • Fulvestrant + AZD2014 (continuous daily schedule) • Fulvestrant + AZD2014 (intermittent schedule - 2 days on, 5 days off) • Fulvestrant + everolimus Randomization will be stratified by the following criteria: • Measurable disease (vs. non-measurable). • Sensitivity to prior endocrine therapy (sensitive versus resistant) Sensitivity to prior endocrine therapy is defined as (i) at least 24 months of endocrine therapy before recurrence in the adjuvant setting or (ii) a complete or partial response to at least one line of prior metastatic endocrine treatment, or (iii) stabilization for at least 24 weeks of at least one line of endocrine therapy for locally advanced and/ or metastatic breast cancer. Treatment will be continued until disease progression unless there is evidence of unacceptable toxicity or if the patient requests to be withdrawn from the study. If one of the treatments (fulvestrant or mTOR inhibitor) is discontinued prior to disease progression, patients should be continued on single agent treatment until progression, evidence of unacceptable toxicity or if the patient requests to be withdrawn from the study. At the time of documented disease progression (using RECIST 1.1), patients randomised to receive fulvestrant + everolimus who still meet eligibility criteria (see Section 5.4. and 5.5.) may be permitted to switch treatment to fulvestrant + AZD2014 (continuous daily schedule). Treatment switch must begin no later than 28 days after the clinic visit at which progression was determined. Patients will receive switched therapy until progression, intolerable toxicity, elective withdrawal from the study, or until the completion or termination of the study, whichever occurs first. Tumour evaluations will be performed before the initiation of treatment, every 8 weeks during the first 40 weeks and every 12 weeks thereafter until disease progression. The study will also assess the relationship between the anticipated anti-tumour activity of the treatment regimen and biological characteristics of patients' tumour at baseline.
Number of patients	A minimum of 300 patients, with at least 90 patients each in the two fulvestrant + AZD2014 arms and 60 patients each in the fulvestrant alone and the fulvestrant + everolimus arms, respectively.

Main eligibility criteria	• Histologically confirmed breast cancer
	• Metastatic and/ or locally recurrent disease
	• Patients must have
	  • at least one lesion, not previously irradiated, that can be measured accurately at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) which is suitable for accurate repeated measurements, or
	  • lytic or mixed (lytic + sclerotic) bone lesions in the absence of measurable disease as defined above; patients with sclerotic/ osteoblastic bone lesions only in the absence of measurable disease are not eligible.
	• ER-positive disease, defined as ER Score ≥3 (Allred) or ≥1% cells (IHC); HER2-negative disease defined as HER2 score of 0-2 on IHC and/or no amplification of the HER2 gene on ISH;
	• Postmenopausal defined as (i) age ≥50 years and ≥1 year of amenorrhea, (ii) age < 50 years and ≥1 year of amenorrhea with an estradiol assay <20 pg/mL, (iii) age < 50 with prior hysterectomy but intact ovaries with an estradiol assay < 20 pg/mL or (iv) status after bilateral oophorectomy (≥ 28 days prior to first study treatment).
	• Disease refractory to AIs, defined as (i) disease recurrence while on, or within 12 months of end of adjuvant treatment with letrozole, anastrozole, or exemestane, or (ii) progression while on, or within one month of end of letrozole, anastrozole or exemastane treatment for locally advanced or metastatic breast cancer
	• FFPE tumour tissue available for central testing
	• ECOG performance status ≤2
	• ANC ≥1500/µl, platelet count ≥100000/µl, haemoglobin ≥9 g/dL, serum creatinine and bilirubin <1.5 x ULN (< 3 times ULN in the presence of liver metastases); AST or ALT <2.5 x ULN; INR< 1.5 x ULN (for patients with therapeutic anticoagulation a stable INR ≤2.5 x ULN is required); aPTT <1.5 x ULN; fasting serum cholesterol ≤ 300 mg/dl; fasting triglycerides ≤ 2.5 ×ULN.
	• No life-threatening metastatic visceral disease; life-threatening metastatic visceral disease defined as extensive hepatic involvement or any degree of brain or leptomeningeal

	involvement (past or present), or symptomatic pulmonary lymphangitic spread. Patients with discrete pulmonary parenchymal metastases are eligible, provided their respiratory function is not compromised as a result of disease. • No more than one line of prior chemotherapy for metastatic breast cancer • No prior treatment with fulvestrant or PI3K/Akt or mTOR inhibitors • No clinically significant abnormalities of glucose metabolism as defined as (i) diagnosis of diabetes mellitus type I (irrespective of management).or uncontrolled diabetes mellitus type II, or (ii) glycosylated haemoglobin (HbA1C) ≥8.0% at screening (64 mmol/mol) • No significant pulmonary dysfunction or cardiovascular disease or uncontrolled diabetes • No current anaemia symptoms (anaemia classed as haemoglobin <90 g/L) • Written informed consent to participate in the trial
Treatment	• Fulvestrant • Fulvestrant + AZD2014 (continuous daily schedule) • Fulvestrant + AZD2014 (intermittent schedule - 2 days on, 5 days off) • Fulvestrant + everolimus
Primary Endpoint	Progression-free survival, defined as the time from the date of randomisation to the date of first documented tumour progression based on investigator assessment (using RECIST 1.1) or death from any cause, whichever occurs first.
Secondary Efficacy Endpoints	• Progression-free survival, defined as the time from the date of randomisation to the date of first documented tumour progression as assessed by an independent review facility [IRF] (using RECIST 1.1) or death from any cause, whichever occurs first. • Objective response, defined as a complete or partial response, based on investigator and IRF assessment (using RECIST 1.1) • Average change (%) in tumour size at 16 weeks compared to baseline, based on investigator and IRF assessment using RECIST 1.1; tumour size is defined as the sum of the longest diameters of the target (i.e. measurable tumour) lesions • Clinical Benefit (CB), defined as number of patients with complete or partial response or stable disease maintained ≥24 weeks, based on investigator and IRF assessment using RECIST 1.1) • Overall survival, defined as the time from date of randomisation to the date of death due to any cause • Duration of response, defined as the time from first documentation of complete or partial response to disease progression based on investigator and IRF assessment using RECIST 1.1 • Duration of clinical benefit, defined as the time from randomisation to disease progression based on investigator and IRF assessment using RECIST1.1 in patients with CB • Percentage change in serum of serum beta C-terminal cross-linking telopeptide of Type I collagen (βCTx) and N-terminal propeptide of Type I procollagen (PINP) from screening/baseline to each time that samples are collected. • Patient reported outcomes, as assessed by the Functional Assessment of Cancer Therapy – General (FACT-G) questionnaire together with the FACT-Anti-A, and FACT-ES subscales[2] • Assess PK parameters of AZD2014 when co-administered with fulvestrant to breast cancer patients • PK assessment of fulvestrant when administered alone and in combination with AZD2014 or everolimus to breast cancer patients

Safety Endpoints	• Incidence of serious adverse events
	• Incidence of grade 3 and 4 adverse events (CTCAE, version 4.03)
	• Incidence of all adverse events of all grades
	• Incidence of the following selected adverse events (any grade)
	  • Hyperglycaemia
	  • Diarrhoea
	  • Stomatitis

[2] Not all patients will contribute to this endpoint. Contribution will be dependent on the availability of the relevant questionnaire in the local language. Refer to section 8.1.3.

- Rash
- Interstitial pneumonitis
- Fatigue

- T-Wave changesAdverse events leading to discontinuation of the study medication
- Changes in vital signs and clinical laboratory results during and following study drug administration

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ABBREVIATIONS LIST

Abbreviation	Definition
AE	Adverse event
AI	Aromatase Inhibitor
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
ATP	Adenosine triphosphate
BSA	Body surface area
CA	Competent Authority
CI	Chief Investigator
CT	Computed tomography
CR	Clinical complete response
CHF	Congestive heart failure
PR	Clinical partial response
CRF	Case report form
CTA	Clinical trials authorisation
CTC	(NCI) Common toxicity criteria
CXR	Chest X-Ray
DCIS	Ductal carcinoma in situ
DPA	Data protection act
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ER	Estrogen receptor
EU	European Union
FACT-G	Functional Assessment of Cancer Therapy-General scale,
FACT-Anti-A	Functional Assessment of Cancer Therapy-Anti-Angiogenesis subscale
FBC	Full Blood Count
FISH	Fluorescence in situ hybridization
GCP	Good clinical practice
GI50	Fifty percent growth inhibition
GLP	Good laboratory practice
H&E	Haematoxylin and eosin
HR	Hazard Ratio
HRT	Hormone replacement therapy
HTA	Human tissue authority
HER2	Human epidermal growth factor receptor 2
ICH	International conference on harmonisation
IEC	Independent ethics committee
IHC	Immunohistochemistry
IMPs	Investigational medicinal products
IRS	Insulin Receptor Substrate
IV	Intravenous
IHC	Immunohistochemistry
LDH	Lactate dehydrogenase
LFTs	Liver function tests
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
MBC	Metastatic breast cancer
MTD	Maximum tolerated dose
mTOR	Mammalian Target of Rapamycin

Abbreviation	Definition
MTORC	mTOR complex
NCC	National Coordinating Centre
NCI	National Cancer Institute
NCRI	National Cancer Research Institute
NCRN	National Cancer Research Network
NIHR	National Institute for Health Research
NYHA	New York Heart Association
PA	Posteroranterior
PARP	poly-ADP ribose polymerase
pCR	Pathological complete response
pCR inv	Pathological residual in situ tumour without evidence of invasive tumour cells
PFS	Progression-free Survival
PROs	Patient Reported Outcomes
PR	Progesterone receptor
PD	Progression
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetic
PTEN	Phosphatase and tensin homolog
pINV	Pathological residual invasive tumour cells
QoL	Quality of Life
QMUL	Queen Mary University of London
RNA	Ribonucleic Acids
RBC	Red blood cell count
SAE	Serious adverse event
SAR	Serious adverse reaction
SERM	Selective ER modulators
SERD	Selective ER downregulators
SUSAR	Suspected unexpected serious adverse reaction
SD	Stable disease
SDV	Source data verification
SLN	Sentinel lymph node
SPC	Summary of product characteristics
TMG	Trial management group
TTP	Time to Progression
TSC	Trial steering committee
ULN	Upper limit of normal
WBC	White blood cell count
WHO	World Health Organisation

1 INTRODUCTION AND STUDY RATIONALE

1.1 Hormone-receptor-positive metastatic breast cancer

Breast cancer is the most common malignancy affecting women in northern Europe and North America, corresponding to an age-corrected annual incidence of 100 to 120 per 100000 females. Although impressive improvements have been made in the adjuvant treatment of early breast cancer, approximately 20-25% of all patients treated with curative intent will develop metastatic disease. The medical treatment of metastatic breast cancer (MBC) offers a wide range of options including chemotherapy, endocrine therapy, treatment with antibodies directed against growth factors relevant to the disease, tyrosine kinase inhibitors, radiation therapy, and supportive measures. The abundance of treatment options has contributed to an impressive amelioration of prognosis in a proportion of patients with MBC. Primary goals of treatment in MBC remain maximizing the quality of life (QoL), prevention and palliation of symptoms and prolongation of survival.

Estrogen and the estrogen receptor (ER) play an important role in the development and progression of breast cancers. Therapeutic strategies directed at inhibiting the action of ER using selective ER modulators (SERMs) such as tamoxifen, withdrawing estrogen by surgical or medical ovarian ablation or by aromatase inhibitors (AIs; such as anastrozole, letrozole, and exemestane), or targeting ER for degradation with selective ER downregulators (SERDs) represent highly successful examples of targeted therapy for clinical breast cancer. Given that approximately 70-80% of invasive breast tumours diagnosed in postmenopausal women are ER-positive and/or progesterone receptor (PR)-positive, advances in endocrine therapy are of enormous clinical relevance for MBC patients.

Endocrine treatment is generally offered as the first treatment option to most women with hormone-sensitive, HER2-negative MBC, whereas chemotherapy is commonly considered after a patient has progressive disease after multiple consecutive endocrine therapy regimens or to control symptomatic visceral disease. This recommendation is based upon lower toxicity of endocrine treatment and generally longer durations of response in this subset as compared with cytotoxic chemotherapy, with no difference in OS. Patients with hormone-sensitive MBC are typically characterized by a relatively long disease-free interval, no or limited visceral involvement, limited metastatic sites and disease-related symptoms and relatively slow disease progression.

Despite the central role of endocrine therapy in the treatment of ER-positive MBC, several key questions remain concerning the optimal endocrine agent and the optimal sequence. Third-generation AIs are often considered the first-line treatment of choice, as they have produced a significant survival advantage compared with tamoxifen, progestogens, and the older AIs in randomised clinical studies [1,2,3,4]. However, these data were largely based on trials before the era of adjuvant AIs and also before the introduction of fulvestrant in the metastatic setting, and questions remain unanswered concerning the sequence of the various endocrine therapies with the current treatment options for early and advanced breast cancer.

Fulvestrant is a first-in-class SERD that interrupts both ligand dependent and independent ER signalling. Fulvestrant, an analog of 17b-estradiol, binds the ER with a similar affinity to estradiol, but disrupts the ER through its alkinylsulphinyl side chain, leading to increased ER degradation and decreased receptor half-life [5]. Unlike tamoxifen, fulvestrant blocks the effect of growth factor signalling via the ER and has no agonist activity. Fulvestrant is currently indicated for the treatment of postmenopausal women with ER-positive locally advanced or MBC that has relapsed or is progressing after prior antiestrogen therapy.

Given its mode of action as well as preclinical and early clinical studies, it was initially expected that fulvestrant would be superior to tamoxifen and other endocrine therapies in the clinic [6,7]. However, several randomised trials comparing fulvestrant with tamoxifen, anastrozole, and exemestane indicated equivalence [8,9,10,11]. In these studies, Fulvestrant was used at the initially approved dose of 250 mg given by intramuscular injection every 28 days. This regimen was subsequently modified; as a first step, a loading dose regimen with Fulvestrant injections on days 1, 15 and 28 and monthly thereafter was introduced to address concerns that with the original regimen steady-state concentrations were only achieved at approximately 3 months which could have resulted in early progression of some patients [12]. In a second step guided by results from preoperative studies, the fulvestrant dose was doubled to 500 mg given on days 1, 15 and 28 and monthly thereafter [13,14].

This higher dose of fulvestrant was subsequently compared to 250 mg monthly in a randomised trial in MBC patients who experienced progression after prior endocrine therapy [15]. High dose of fulvestrant (500 mg) significantly prolonged PFS compared to the 250 mg dose with a median progression-free survival (PFS) of 6.5 months compared to 5.5 months (HR 0.80; 95%CI: 0.68-0.98; p = 0.006). More specifically, in this trial, subgroup analysis showed that PFS was prolonged in patients who had recurred or relapsed during anti-estrogen therapy

(median PFS 8.6 vs. 5.8 months; HR 0.76; 95%CI: 0.62-0.94; p = 0.013) or during AI therapy although not reaching statistical significance for the latter (median PFS 5.4 vs. 4.1 months; HR 0.85; 95%CI: 0.67-1.08; p = 0.195).

This is further supported by the results of an open-label randomised phase II study comparing fulvestrant 500 mg with anastrozole in patients previously untreated for advanced breast cancer demonstrating a significantly improved time to progression (TTP) for fulvestrant (fulvestrant, median TTP 23.4 months versus Anastrozole, median TTP 13.1 months; HR 0.66; 95% CI, 0.47 to 0.92; p = 0.002) [16].

As a result of these findings, the approved dosing for fulvestrant has been changed and fulvestrant 500 mg monthly with 500 mg loading dose on day 14 is now the approved dose in both the US and Europe for ER-positive MBC following disease relapse after anti-estrogen.

1.2 Aberrant activation of the PI3K/Akt/mTOR-pathway in endocrine resistance

Despite all this progress in endocrine treatment, it is still only a subgroup of patients that will derive the optimal therapeutic benefit, whereas other patients have refractory disease or will develop drug resistance during treatment. Over the last years, a great deal of basic and translational research has been directed at elucidating the processes of resistance and several studies indicate that acquired resistance to endocrine therapy is a progressive, step-wise phenomenon induced by the selective pressure of hormonal agents, which leads breast cancer cells from an estrogen-dependent phenotype, that is responsive to endocrine manipulation, to a non-responsive phenotype, and eventually to an estrogen-independent phenotype. Several different mechanisms have been hypothesized to be involved in developing resistance of breast cancer cells to hormonal therapy, including molecular cross talk between ER, PR, and growth factor-receptor signalling pathways, estrogen hypersensitivity associated with increased transcriptional activity of ERα and the relationship between the classical and non-classical, non-genomic effects of ER in breast cancer cells.

An emerging mechanism of endocrine resistance is aberrant signaling through the phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR signalling pathway [17,18]. There is increasing evidence of a close interaction between the PI3K/Akt/mTOR pathway and ER signalling. One of the main substrates of the mTOR complex 1 (mTORC1), S6 kinase 1, has been shown to phosphorylate the activation function domain 1 of the ER, leading to ligand-independent ER activation [19,20].

Abnormal activation of the PI3K/mTOR pathway in cancer, either via genetic alterations in PI3K pathway constituents [PI3K-activating mutations or genetic amplification, loss of the antagonistic tumour suppressor Phosphatase and tensin homolog (PTEN)] or via the transduction of aberrant receptor tyrosine kinase (RTK) signals, is a common finding in a variety of tumour types. Aberrant PI3K pathway activation frequently occurs in breast cancer, most commonly through activating mutations of the PI3K catalytic subunit (PI3KCA) or inactivation of the negative regulator PTEN [21,22,23,24]. Approximately 43% of ER-positive breast cancer patients have mutations in PIK3CA, the alpha subunit of PI3K (or p110a), and an additional 5-10% have loss of PTEN protein expression (PTEN null). PIK3CA mutations are more frequently found in Luminal A cancers (46%) than Luminal B tumours (29%) [25]. Additional pathway abberrations such as Akt1 mutations, loss of INPP4B, or PIK3Ca amplifications have been described in ER-positive breast cancer, with aberrations of different pathway components being generally mutually exclusive in breast cancer tumour samples. All these alterations result in up-regulation of the PI3K pathway [26,27] and make human breast cancer a rational target for PI3K inhibitors. Activation of the PI3K pathway has been associated with poor prognosis and resistance to endocrine therapy in ER-positive tumours [28,29,30,31,32,33].

Multiple lines of investigation have demonstrated that downregulation or inhibition of PI3K or mTOR activity can overcome endocrine resistance [34,35,36]. Importantly, estradiol can suppress apoptosis induced by PI3K knockdown or inhibition in ER-positive breast cancer, suggesting independent PI3K-dependent and estradiol-dependent cell survival mechanisms [37]. Preclinical studies demonstrate synthetic lethality of PI3K/mTOR pathway inhibition and estrogen deprivation, providing a strong rationale for the combination of PI3K inhibitors and endocrine therapy [37,38]. It has furthermore been shown that PIK3CA wild-type or mutant tumours equally benefit from combined PI3K/Akt/mTOR pathway inhibition and endocrine therapy, suggesting that eligibility in clinical trials should not be restricted by PIK3CA mutation status [37]. This combined with the association of therapeutic resistance with increased PI3K pathway signalling suggests that inhibition of PI3K/Akt/mTOR signalling could have broad applications in the treatment of breast cancer.

1.3 mTORC1 inhibitors in ER-positive metastatic breast cancer

The PI3K-AKT-mTOR pathway functions as a sensor of mitogen, energy and nutrient levels and is a central controller of cell growth. Although mTOR has not been found to be mutated in human cancers, the PI3K/AKT/mTOR pathway is one of the most frequently activated pathways in human tumours. This occurs either by mutation/up-regulation of upstream proteins (such as PI3K or AKT) or through loss of the PTEN tumour

suppressor (mutation or epigenetic silencing). mTOR has been identified as a downstream target of PI3K, AKT and Ras signalling pathways.

The mTOR kinase is the catalytic component of two distinct multiprotein complexes, mTORC1 and mTORC2, defined by their associated proteins. Both complexes have different cellular functions. In addition to mTOR, mTORC1 contains the proteins RAPTOR, mLST8, and PRAS40. mTORC1 activates p70S6K and 4EBP1, which in turn activate the ribosomal protein S6 and eIF4E, both involved in protein translation. mTORC1 drives cellular growth by controlling numerous processes that regulate protein synthesis and degradation. mTORC2 also contains mLST8, but instead of RAPTOR and PRAS40, mTORC2 contains the RICTOR, mSIN1, and PROTOR proteins [39,40,41]. mTORC2 phosphorylates AKT on Ser 473, increasing its activity. It also phosphorylates proteins involved in the cytoskeleton such as paxillin. mTORC2 therefore contributes to cellular proliferation.

Regulation of the mTOR pathway involves a feedback loop whereby S6K1 catalyses the phosphorylation of insulin receptor substrate (IRS) proteins, targeting them for degradation by the proteosome. This prevents IRS proteins from activating PI3K, thereby inhibiting activation of AKT. Regulation of mTOR activation also involves the LKB1/AMPK cascade, regulating TSC2/TSC1 activity in conditions of restricted energy.

Sirolimus (formerly called rapamycin) and its derivatives, the so called rapalogues (everolimus [RAD001] or temsirolimus [CCI-779]) inhibit mTOR through allosteric binding to mTORC1, leaving mTORC2 unregulated. Rapalogues are currently being extensively investigated in human cancers and have received approval for the treatment of renal cell cancers, neuroendocrine tumours of pancreatic origin, and ER-positive MBC.

There is increasing evidence that inhibition of only mTORC1 sets off a negative feedback mechanism exerted by S6K via PI3K that leads to increased Akt signalling. The elevation in pAKT may at least in part explain the disappointing results with the rapamycin derivatives in many solid tumours and activation of this feedback loop is associated with a shorter time to progression in PTEN null glioblastoma patients treated with rapamycin [42].

Everolimus (Afinitor), a sirolimus derivative that inhibits mTOR through allosteric binding to mTORC1, has been evaluated in several clinical trials in HR-positive breast cancer in combination with endocrine treatments. In a randomized, phase 2 study involving newly diagnosed ER-positive breast cancer neoadjuvant everolimus combined with letrozole improved the clinical response rate and decreased tumour-cell proliferation as compared with letrozole alone [43]. In a more recent MBC study involving 111 postmenopausal women with ER-positive advanced breast cancer previously treated with an AI, the combination of everolimus and tamoxifen was associated with significantly improved progression-free survival relative to tamoxifen alone (8.6 months vs. 4.5 months, P = 0.002) and with significantly improved overall survival (median not reached vs. 24.4 months, P = 0.01) [44].

Finally, data from the Phase III BOLERO-2 study demonstrated that the addition of everolimus to exemestane more than doubled PFS compared with single-agent exemestane in ER-positive, HER2-negative MBC patients whose disease was refractory to prior treatment with letrozole or anastrozole (median PFS 11.0 versus 4.1; HR = 0.38, 95% CI 0.31-0.48, p <0.0001) [45]. Randomisation was stratified by documented sensitivity to prior hormonal therapy and by the presence of visceral metastasis. Sensitivity to prior hormonal therapy was defined as either (1) documented clinical benefit (complete response, partial response, stable disease ≥24 weeks) from at least one prior hormonal therapy in the advanced setting or (2) at least 24 months of adjuvant hormonal therapy prior to recurrence. The observed effects were similar accorss all subgroups, including age, sensitivity to prior hormonal therapy, number of organs involved, status of bone-only lesions at baseline and presence of visceral metastasis, and across major demographic and prognostic subgroups with an estimated hazard ratio ranging from 0.25 to 0.60. No differences in the time to ≥5% deterioration in the global and functional domain scores of QLQ-C30 were observed in the two arms. Some might query however whether or not the most appropriate patient reported outcome measures (PROs) in this particular setting, had been employed.

Taken together, these studies suggest that everolimus adds to the anticancer activity of antiestrogen therapy in a variety of clinical settings especially in endocrine resistance and with different classes of endocrine agents. Everolimus is approved for the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal AI.

In contrast to the encouraging findings with everolimus are the results of a randomised study with the TORC1 inhibitor temsirolimus. In the HORIZON study [46}, 1116 patients with ER-positive MBC, who had not received endocrine treatment for advanced disease, were treated with letrozole or letrozole plus temsirolimus, given on an intermittent schedule with for 5 days of treatment every 2 weeks. The trial was designed to detect a 25% improvement in median PFS for the combination. However, after the second planned interim analysis with 380 PFS events, the trial was stopped as there was no difference in PFS (HR 0.89, 95% CI 0.75-1.05, p=0.18; median PFS 8.8 versus 8.9 months) and the IDMC advised that the trial was unlikely (<10% chance) to meet its primary objective. Full results have not been reported but the available data suggest a potential benefit in women under the age of 65 years (HR 0.74, 95% CI 0.59-0.92, p=0.006; median PFS 9.0 versus 5.6 months). More patients in the

combination experienced grade 3 adverse events and required dose modifications or discontinued the treatment due to AEs [46]. Potential explanations for the negative outcome of this study include the intermittent drug schedule selected for this study as well as the patient population on study with predominantly hormone-naïve patients, whereas BOLERO-2 included more than 80% of patients with secondary hormone resistance.

1.4 Investigational Agent: AZD2014

AZD2014 is an ATP-competitive, selective mTOR kinase inhibitor targeting both mTORC1 (rapamycin-sensitive) and mTORC2 (rapamycin insensitive) complexes. AZD2014 is molecularly different from rapalogues and achieves more profound mTORC1 inhibition, in particular inhibiting phosphorylation of the rapamycin insensitive site on 4E-BP1 (T37/46). AZD2014 also inhibits mTORC2 and has a broader range of growth inhibitory activity *in vitro* across tumour types compared to rapalogues. As such, dual TORC1/TORC2 inhibitors like AZD2014 that inhibit both mTOR complexes may offer therapeutic advantages to rapalogues.

AZD2014 has a short half-life compared to other mTOR inhibitors (especially rapalogues). This enables intermittent high dose schedules of AZD2014, delivering maximum target inhibition for a relatively short time which may improve the risk/benefit profile. In preclinical in vivo models, both intermittent (20 mg/kg BD 2 days on, 5 off) and continuous (15 mg/kg OD) dosing schedules are equally efficacious. A weekly dosing schedule of AZD2014 has been very well tolerated in early clinical trials with a potentially better PK profile compared to BD continuous dosing. The geomean (n=3) clinical exposure for the weekly dosing schedule (680mg/week dosed for 2 days 170 mg BD, 5 off) is double the efficacious exposure predicted from preclinical models however the numbers are small (patient recruitment ongoing).

AZD2014 is especially effective in ER-positive breast cancer cell lines and xenograft models, showing substantial activity both in hormone-sensitive and resistant models. Preliminary data from the currently recruiting clinical phase I trials are showing 5 PRs in ER-positive breast cancer patients, one in the mono therapy trial and four in combination with Fulvestrant (with one nearly CR with disappearance of the target lesions plus stable residual disease in a non-target lesion) and one PR in a patient with pancreatic acinar type cancer on mono-therapy. An additional 7 patients have been reported with clinical benefit including 5 patients with breast cancer (4 patients with ER-positive MBC, 1 patient with HER2-positive disease) and 2 patients with endometrial like cancers, out of a total of 66 patients to date.

1.4.1 Non-clinical information and correlative studies

AZD2014 is a specific inhibitor of mTORC1 and mTORC2 in enzyme assays and inhibits the phosphorylation of AKT substrates in cells. AZD2014 inhibits the proliferation of a range of cell lines derived from solid and haematological tumours. ER-positive breast cancer cell lines appear to be the tumour types that show the greatest sensitivity to AZD2014, with substantial activity both in hormone-sensitive and resistant models. AZD2014 shows dose dependent pharmacodynamic and antitumour activity in xenografts at well-tolerated doses.

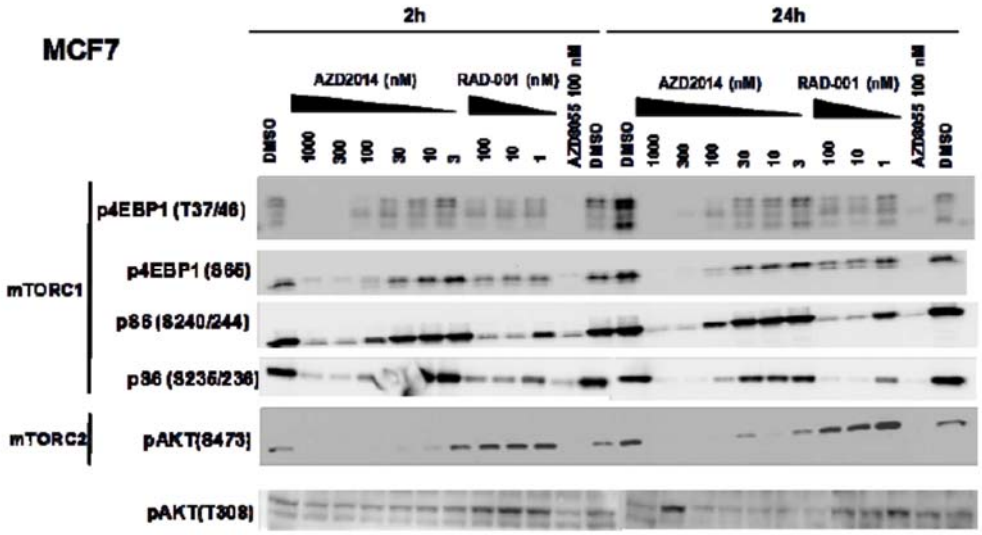
Studies *in vitro* show AZD2014 to be a potent inhibitor of mTOR (IC50 value of 2.81nM using a truncated FLAG-tagged mTOR alpha screen assay). In a counter screen against 220 other kinases, AZD2014 was inactive, including PI3Kα-δ using recombinant PI3 kinases with the lipid phosphatidylinositol bisphosphate as substrate. The IC50 for the different PI3Ks tested were all greater than 3 μM indicating at least a 1000-fold selectivity.

In cell lines, AZD2014 inhibited downstream targets of both mTORC1 (phosphorylation of pS6 at serine 235/236 and serine 240/244; phosphorylation of 4EBP1 at tyrosine 37/46 and serine 65) and mTORC2 (phosphorylation of AKT at serine 473) in a dose- and time-dependent manner. In a panel of ER-positive breast cancer cell lines, AZD2014 induced a concentration-dependent, sustained decrease of pAKT (S473), pS6 (S240/244 and S235/236) and p-4EBP1 (S65 and T37/46), confirming substantial activity against mTORC1 and mTORC2 downstream targets (Figure 1a). In contrast, RAD001 potently inhibited S6 phosphorylation, but had only a modest effect on the phosphorylation of 4EBP1 at S65 (normally rapamycin-sensitive) and no apparent activity against the phosphorylation of 4EBP1 at T37/46 (rapamycin-resistant). The fact that AZD2014 more potently inhibited 4EBP1 phosphorylation than RAD001 was reflected in the observation that AZD2014 blocked more efficiently translation initiation and had a greater impact on protein expression of Cap-dependent genes such as Mcl-1, c-Myc and cyclin D1. Finally, RAD001 increased pAKT S473 and pAKT T308 suggesting that the feedback loop between S6K and insulin receptor substrate (IRS1) is functional in these cells, whereas it was effectively inhibited with AZD2014 due to its mTORC2 activity.

Both, AZD2014 and rapamycin inhibited the proliferation of the majority of cell lines within a large cell panel of solid tumour and haematological cell lines, including 24 breast cancer cell lines, in a dose-dependent manner. Fifty percent growth inhibition (GI50) was observed at sub-micromolar concentrations in 72 out of 82 cancer cell lines with AZD2014. In similar conditions, GI50 lower than 1 μM were observed in only 38 out of 83 cell lines with rapamycin. In these studies, AZD2014 induced more complete growth inhibition than rapamycin (Figure 1b). ER-positive breast cancer cell lines appear to be the tumour type that shows the greatest sensitivity to AZD2014 as

monotherapy *in vitro.* AZD2014 induced complete growth inhibition in several ER-positive cell lines where RAD001 induced only partial inhibition of cell growth (Figure 1c). Exposure to AZD2014 also resulted in cleavage of poly-ADP ribose polymerase (PARP) which suggests induction of apoptosis, whereas PARP cleavage was not observed with RAD001. Interestingly, AZD2014 demonstrated similar and in some cases superior cytotoxicity and inhibition of proliferation in ER-positive cell lines with acquired resistance to tamoxifen, fulvestrant or long-term estrogen deprivation compared to the parental hormone-sensitive cell lines.

a)



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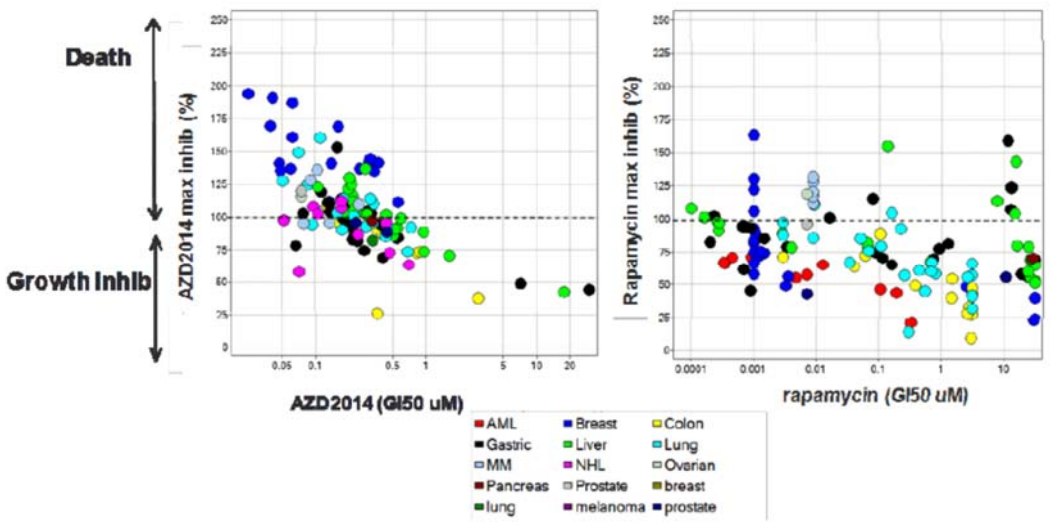

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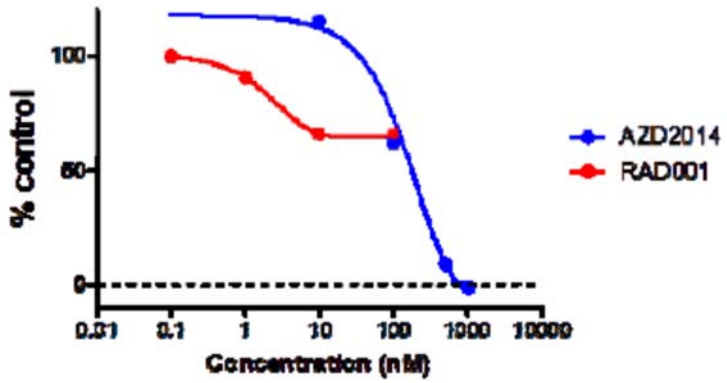


Figure 1: AZD2014-induced *in vitro* mTOR biomarker modulation and inhibition of proliferation

a) mTOR biomarker modulation in MCF7 cells (representative immunoblotting) with AZD2014 relative to RAD001; b) growth inhibition and cytotoxicity with rapamycin and AZD2014 in a solid tumour and haematological malignancy cell line panel; c) Inhibition of cell proliferation in ER+ MCF7 breast cancer cells with AZD2014 versus RAD001

AZD2014 induces a dose-dependent tumour growth inhibition in xenograft models grown in immunocompromised animals at well tolerated doses. In nude mice bearing ER-positive MCF7 breast cancer xenografts, the tumour growth inhibition was 29%, 72% and 111% at 3.75, 7.5, and 15 mg/kg once daily, respectively. In the same ER-positive MCF7 breast cancer xenografts model, intermittent weekly adminstration of AZD2014 resulted in at least comparable tumour growth inhibition vs continuous daily dosing (Figure 2a).

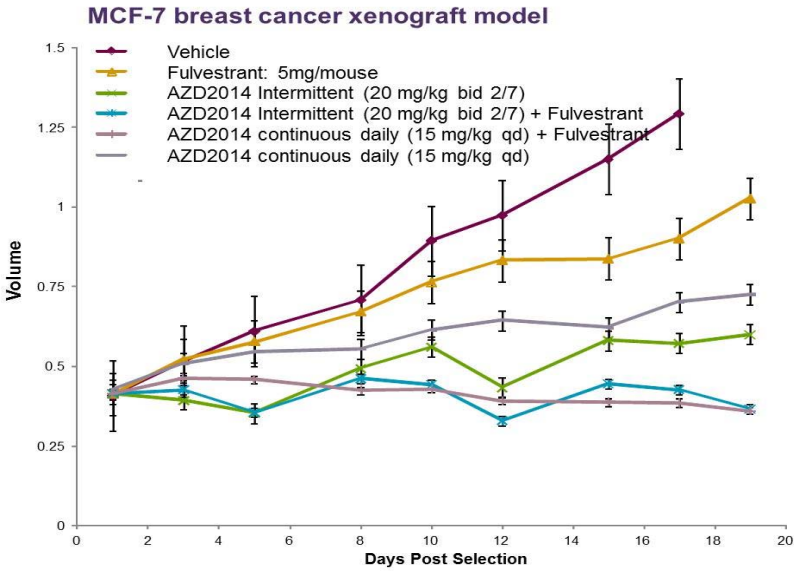
Both p4EBP1 and pS6 were strongly modulated by AZD2014 at the peak concentration with more than 90% decrease in overall staining (Figure 2b). Inhibition was still greater than 50% at 8 hours post dose with full recovery by 24 h. The biomarker profile was very similar at steady state (after 4 daily doses).

In a different ER-positive breast cancer xenograft model (HBCx3 explant) representing HER2-negative luminal B disease with high levels of proliferation markers (Ki67, 60%) and high levels of Her3 and pAKT T308, AZD2014 was administered once daily alone or in combination with tamoxifen weekly (Figure 2c). As previously observed, the HBCx3 explant model was resistant to tamoxifen. AZD2014 completely inhibited tumour growth but no additional effect was observed in presence of tamoxifen. The antitumour effect was associated with modulation of mTORC1 markers (pS6, p4EBP1) and mTORC2 (pAKT Ser473, pNDRG1). Tamoxifen by itself had no impact on the mTOR biomarker levels. Similarly, there was no difference in biomarker levels with AZD2014 alone and in combination with tamoxifen.

The modulation of pS6 (Ser235/236) and p4EBP1 (T37/46), both markers of mTORC1 activity, and pAKT(Ser473), marker of mTORC2 activity, was explored in several preclinical models. A good relationship was observed between the biomarkers of mTORC1 (pS6 and p4EBP1) and mTORC2 (pAKT) and free plasma concentrations. Pharmacokinetic-pharmacodynamic relationships showed that 50% inhibition of phosphorylation of AKT is obtained

in U87-MG xenografts for total drug plasma concentrations greater than 0.5 µM. Across multiple preclinical models, the antitumour efficacy appeared to be related to the duration of the biomarkers modulation.Further details are provided in the Investigators' Brochure.

a)



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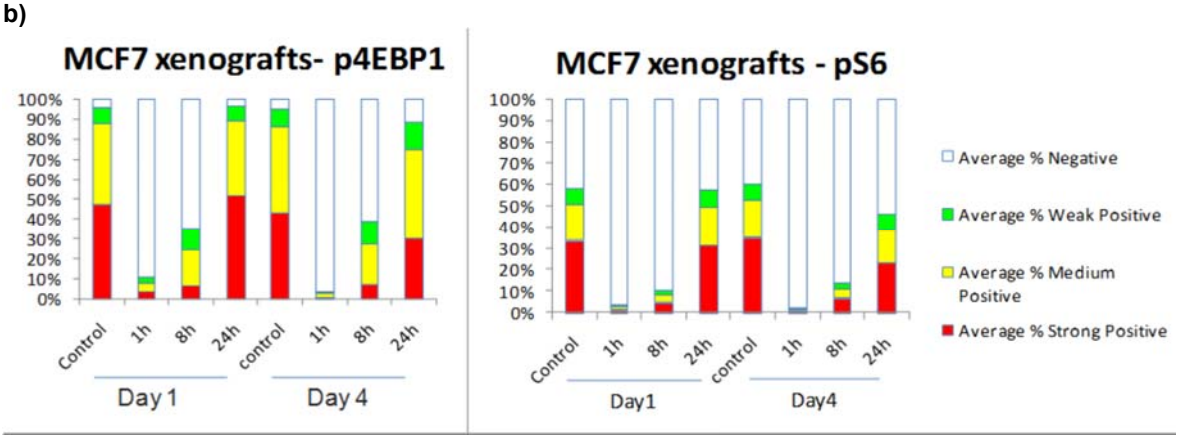

c)

Figure 2: In vivo activity and pharmacodynamics effects of AZD2014 in ER-positive breast cancer xenografts

a) Intermittent weekly versus continuous daily dosing of AZD2014 in MCF7 breast cancer xenograft model; b) mTORC1 (p4EBP1 and pS6) biomarker modulation in MCF7 breast cancer xenografts after administration of AZD2014; c) Antitumour activity and biomarker modulation in HBCx3 xenografts after administration of 15 mg/kg AZD2014 once daily alone and in combination with tamoxifen 4 mg/kg weekly

1.4.2 Clinical information

AZD2014 has been administered to patients with advanced cancer in 2 ongoing Phase I studies either as solution or using a tablet formulation (D2770C00001, D2270C00005) investigating the appropriate dose level for clinical use. In the monotherapy study, during Part A, patients received a single dose of 25 mg, 50 mg, 70 mg or 100 mg AZD2014 on Day 1, followed by a washout period of a minimum of 48 h up to a maximum of 7 days, and then by continual BD dosing of AZD2014 thereafter. During Part B patients received 50 mg as continuous BD dosing. A dose of 50 mg BID was declared as maximal tolerated dose (MTD) for continuous dosing schedules in this study.

A once daily and an intermittent weekly (2 days on, 5 days off) dosing schedule are currently being explored. The once daily schedule had been stopped due to unfavourable safety and PK profiles but interestingly the intermittent

weekly schedule has been very well tolerated with a potentially better PK profile compared to BD continuous dosing.

In a single agent study of AZD2014, 11 patients have been dosed at 170 mg (2 days on, 5 days off; total weekly dose of 680 mg) with two patients to date experiencing dose limiting gastro-intestinal toxicity. At a dose level of 125 mg, 6 patients have been dosed without experiencing a dose limiting toxicity so far, hence this dose is considered to be tolerated and and is the recommended Phase 2 dose. This intermittent schedule achieved a total weekly dose of 500 mg compared to 700 mg per week for 50 mg BID continuous.

In the combination Phase I study with Fulvestrant (D2270C00005), patients received a single dose of 35 mg or 50 mg on Day 1, followed by a washout period of a minimum of 48 h up to a maximum of 7 days, and then by continual BD dosing of AZD2014 thereafter. 50 mg BID was declared as MTD for continuous dosing schedules in this study. An intermittent weekly schedule (2 days on, 5 days off) is currently beeing explored,

Safety, Phase I monotherapy (D2770C00001: At doses of 70 mg BD and 100 mg BD, dose-limiting toxicities of fatigue/lethargy, weight loss and mucositis (CTCAE grade 2-3) were reported and these doses of AZD2014 have been declared as non-tolerated. The adverse events that defined its non-tolerability were generally reversible within 1 day to 1 week by cessation. A safety expansion phase (Part B) of up to 70 patients is being conducted to define further the safety profile of AZD2014 AZD2014 at 25 and the maximum tolerated dose of 50 mg BD.

Based on preliminary unvalidated data, the most commonly occurring adverse events are in keeping with those expected in patients enrolled in Phase I oncology studies or in patients receiving rapamycin analogues. The majority of adverse events have been CTCAE grade 1 or 2. The most commonly reported Adverse Events (AEs), regardless of dose or causality, to date are fatigue, nausea, mucositis, decreased appetite, diarrhoea, rash, constipation, vomiting, dyspnoea and cough. The AEs improved in severity or resolved completely within a 1 day up to 1 week after the drug was stopped or dose reduced and therefore a relationship with AZD2014 is likely.

At the MTD of 50 mg AZD2014 BD the drug was generally well-tolerated in most patients. Overall, sixty percent of patients tolerated the drug without AEs and the longest time on treatment was >320 days for 1 patient, who still continues on treatment, and 217 and 183 days for 2 other patients, respectively. The most common events were fatigue, nausea, mucositis, rash constipation, vomiting, dyspnoea and cough (CTCAE grade 1-2) which improved in severity or resolved completely within 1 day up to 1 week after the drug was stopped or dose reduced. These AEs either in combination or as single AEs with higher severity (CTCAE grade 2) resulted in permanent treatment stop in 7 patients (18%), in temporary dose interruptions in 5 patients (12%), and in dose reductions in 2 patients (5%). Twenty one SAEs of grade 3 and above were reported; of these 4 were considered by the investigator to be causally related to AZD2014: fatigue, mucositis, nausea, and rash.

Other clinically important events reported were ECG repolarisation changes.These ECG repolarisation changes comprising progressive T-wave flattening were seen in 4 of the 54 patients at the dose levels of 70 mg (1 patient) and 50 mg (3 patients). In 3 of those patients who continued on treatment the flattening progressed to T-wave inversion. These findings occurred slowly, starting from minimal T-wave flattening to inversions over several weeks, stayed at negative values for several weeks and returned back to low/normal over a period of weeks while on treatment. The patients with these findings showed no clinical signs and symptoms of compromised cardiac function or any elevations in cardiac enzymes. Thirty-day follow-up ECGs were available for 2 patients. ECGs of one patient returned back to normal values and ECGs of another patient the limb leads were very similar to baseline but the chest leads stayed generally smaller in amplitude and remained inverted in V2 and V3. The pathomechnism of the T-wave abnormalities is currently not known and this safety topic will continue to be kept under close surveillance.

A high number of respiratory events (24% patients with dyspnoea, 22% patients with cough, and 17 % lower/upper respiratory tract infections) were reported at 50 mg BD. All reported pulmonary events were analysed retrospectively in detail in regard to signs of pneumonitis, but radiological assessments showed no signs indicative for pneumonitis and additionally the AEs were confounded by other factors, like anaemia, lung metastasis and infections and/or chest wall infiltration. Several patients had low lymphocytes counts from baseline, however no worsening while on treatment was observed for these patients and this does not appear to have contributed to the incidence of respiratory events. Originally pneumonitis was reported as a possible class effect of mTOR inhibitors with an incidence of 5%-36%, however, current detection rates place the risk of pneumonitis as low and therefore baseline thorax scans should provide sufficient safety monitoring. There is so far no sign that AZD2014 would cause pneumonitis, although the number of patients treated so far does not allow final conclusions.

In laboratory parameters, insulin and glucose elevations CTC grade 1-2 have been observed in some patients, a finding frequently described with other mTOR inhibitors. The most prominent haematological findings were lymphopenia in 54% of patients (CTC grade 1-3 in 17% of patients at each grade), anaemia in 28% of patients (mainly CTC grade 1; 1 patient with grade 3), leukopenia in 21% of patients (mainly CTC grade 1), neutropenia in 15% of patients (CTC grade 1-2), and thrombocytopenia in 15% of patients (all CTC grade 1). At the next lower dose level at 25 mg BD, the incidence of anaemia and lymphopenia was also high (67%), but there were no findings of leukopenia, neutropenia and/or thrombocytopenia.

Transaminase increases of CTC grade 1-2 and high values of gamma-glutamyl transferase were reported in single patients, and one patient had a grade 2 bilirubin elevation. All patients (except 2) with AST/ALT/bilirubin changes had liver metastases.

Preliminary data for the intermittent schedule (2 day on, 5 days off) demonstrate a safety profile that appears comparable if not favourable to continuous daily dosing. At 225 mg BID (2 days on, 5 days off), two DLTs were observed (CTC grade 2 nausea and fatigue; CTC Grade 3 fatigue), which improved to tolerable levels (CTC grade 1) when one of the patients was dose reduced to 170 mg/dose. At the dose level of 170 mg/dose, a total of 11 patients have been dosed to date. Dose limiting toxicity has been observed in two patients so far receiving single agent AZD2014 (CTC grade 3 diarrhoea; CTC grade 3 nausea/emesis). At the dose of 125 mg/dose, which is the dose that has been selected for the combination study, the safety profile of the intermittent schedule for AZD2014 monotherapy compares favourably to the continuous daily dosing schedule (50 mg BD) for AZD2014 monotherapy or to rapalogues, with grade 1/2 nausea and fatigue being the main adverse events, These side effects were clinically well manageable. Interestingly no rash and mucositis have been observed so far on any dose level of the intermittent schedules, which is rather unusual with an incidence rate of around 60% with continuous dosing (unvalidated data). The patient longest on treatment so far has been dosed at 170 mg/dose (680 mg/week) for 7 cycles.

Safety, Phase I combination (D2270C00005): preliminary unvalidated data suggest that the overall safety profile of AZD2014 in combination with Fulvestrant is broadly similar to the safety profile observed for monotherapy.

Efficacy: In the monotherapy study, one patient with pancreatic cancer has demonstrated a partial response as assessed by the response evaluation criteria in solid tumours (RECIST), and several patients experienced stable disease with the longest duration of response being 320 days, 217 days and 183 days, respectively. Another partial response was observed in a patient with ER-positive breast cancer.

In the combination study, 3 patients with ER-positive MBC have experienced a partial response, one of them with a complete resolution of target lesions. Additionally 3 patients showed clinical improvement, with one of these patients responding to the combination of AZD2014 and Fulvestrant after progressing on Fulvestarnt single agent treatment. All but one of these patients are still on treatment, including the patient, who developed PD on Fulvestrant monotherapy, who is currently on day 234 of the combination treatment.

In terms of pharmacodynamic reponse in the monotherapy study, at a dose of 50 mg BD AZD2014 reduced cytoplasmic pS6 (S235/236) immunohistochemistry staining in 8 of 10 evaluable paired tumour biopsies confirming that the drug has mTORC1 activity. A reduction in cytoplasmic pS6 (S235/236) was observed in 8 out of 8 tumour biopsies obtained after 1 to 5 hours of therapy. In three of these tumours phosphorylation of S6 was profoundly reduced, falling to below the limit of reliable detection following treatment. Phosphorylation of 4EBP1 (T37/46), a mTORC1 phosphorylation site that is not inhibited by everolimus, was decreased post treatment in 3 out of 9 evaluable paired biopsies. In 2 of these cases total levels of 4EBP1 were also lower in the post treatment biopsies. In peripheral blood monocytes, the fold change in p4EBP1 positive cells at 2 hours post 50 mg dose was 0.43 (90% CI 0.20-0.93). This decrease was not statistically significant.

Phosphorylation of AKT (S473) was significantly inhibited in platelet rich plasma providing evidence for TORC2 inhibition in surrogate tissue. A median change of 66% (90% CI, 78, 60 $p<0.001$) was observed at 2 hours after treatment with 50 mg AZD2014. At 6 to 8 hours post 50 mg dose the median change was 42% (90% CI, 56, 35 $p<0.001$). There was no evidence for an elevation in cytoplasmic pAKT (S473) (mTORC2 phosphorylation site) in 11 tumour biopsies indicating that AZD2014 may be differentiated from everolimus which has been reported to increase phosphorylation on this site in approximately 50% of cases. In tumour biopsies, phosphorylation of AKT (S473) was lower in the post-treatment biopsies in 3 out of 6 evaluable samples. A lower level of pAKT (T308) was also observed after treatment in 2/8 tumour biopsies. An average reduction of 25 units in H score was measured (90% confidence interval of 6-44 unit reduction).

Pharmacodynamic response data for the combination trial will be available in July/August 2013.

Pharmacokinetics: The key single-dose and steady-state pharmacokinetic (PK) findings for AZD2014 administered as monotherapy based on preliminary unvalidated data from Studies D2270C00001 and D2270C00005 are summarized below:

Following a single dose and twice daily [BID] or once daily [QD] continuous dose schedules, AZD2014 administered as a solution formulation is orally available and rapidly absorbed, with median time to maximum plasma concentration [tmax] between 0.5 and 1.5 hours across the 25mg to 125mg dose range. Elimination half-life [$t_{1/2}$] is short and variable between patients (mean = 3.3 hours, range 0.9 – 9.1 hours). Single dose exposure is greater than proportional across the dose range investigated with a 5-fold increase in dose from 25 to 125 mg giving approximately a 13-fold increase in geomean exposure [AUC)]. Non proportionality at steady state is less easy to assess due lack of PK data across as wide a dose range. Inter-patient exposure for any given dose is highly variable (at the 50mg BID maximum tolerated dose the coefficient of variation [CV%] is 54% and 83% respectively for the steady state maximum plasma concentration [Cmax,ss] and area under the curve [AUCss]).

Thus, whilst geomean exposures increase with increasing dose, there is marked overlap within the range of individual patient exposures across the dose levels.

AZD2014 has a low apparent Volume of Distribution [Vss/F] (from 17.5 to 132 L across all doses). The bioavailable fraction [F] is unknown as no human intravenous PK data have been generated. Adverse Events and biomarker modulation suggest the compound distributes to tissues. Apparent clearance from the body is low (CL/F following single doses ranges from 3.87 to 31.8 L/hr [64.5 to 530 mL/min] and CLss/F following BID and QD continuous dosing ranges from 1.04 to 39.7 L/h [17.3 to 662 mL/min]. There is greater than expected accumulation following multiple dosing of AZD2014 in some patients with accumulation rate [RAC] values up to 3.2 (9.5 with high outlier) being seen compared with the expected average of 1.1. The single dose PK data are not predictive of the steady state kinetics in many patients with Tc values up to 3.2 (9.4 with high outlier) being seen compared with the expected 1.0.

Whilst numbers of patients are small and variability high, emerging data indicate that the PK profile for the tablet formulation is different than that for the solution formulation with a slower absorption rate, indicated by a lower geomean peak plasma concentration [Cmax] and longer geomean time to peak [tmax)] than for the same dose of solution, but with a similar overall extent of exposure [AUC] for doses up to 125mg. Limited data at higher doses [175mg] suggest exposure is lower for the tablet than would be predicted for the same dose of solution, probably due to solubility / dissolution rate limited absorption.

The PK profile of an intermittent dosing schedule of the tablet formulation (BID for 2 days followed by 5 days off drug) has been evaluated in a limited number of patients. Early data indicate that similar weekly exposures can be achieved with a tolerated intermittent weekly schedule [170 mg BID 2/5] to those for the maximum tolerated BID continuous tablet dose [50mg BID] with higher peak plasma concentrations achieved in the first 2 days of the week.

PK data for AZD2014 combined with fulvestrant intra-muscular monthly injections indicate no marked difference in exposure to that for AZD2014 monotherapy.

Whilst there is a direct relationship between dose and tolerability, no clear relationship has been yet established between exposure [PK] and safety or efficacy, although total exposure and time above a minimum threshold concentration seem important for efficacy

2 TRIAL OBJECTIVES

2.1 Aims

The main aims of this study are to:

- Determine whether dual inhibition of mTORC 1 and mTORC2 with AZD2014 will increase the anti-tumour activity of endocrine treatment with fulvestrant in ER-positive advanced or metastatic breast cancer.
- Determine whether inhibition of both mTORC 1 and mTORC2 using AZD2014 (will have superior anti-tumour activity compared to inhibition of mTORC1 alone with everolimus, when combined with fulvestrant.
- Evaluate the efficacy and safety of an intermittent schedule of AZD2014 relative to continuous daily dosing of AZD2014
- Explore whether additional efficacy is likely to be present in a subgroup with PI3K-pathway activation for whom it is hypothesised that there will be greater sensitivity to mTOR inhibitors
- Characterize the patient population who might benefit from fulvestrant plus AZD2014 to identify potential predictors of sensitivity

2.2 Primary objective

The primary objective of this study is to:

- Estimate the clinical benefit of fulvestrant + AZD2014 (continuous daily schedule) relative to fulvestrant alone, as measured by investigator-assessed progression-free survival (PFS)

2.3 Secondary objectives

The secondary objectives of this study are to:

- Estimate the clinical benefit of fulvestrant + AZD2014 (continuous daily schedule) relative to fulvestrant + everolimus, as measured by investigator-assessed PFS
- Estimate the clinical benefit of fulvestrant + AZD2014 (intermittent schedule) relative to fulvestrant + everolimus or fulvestrant alone, as measured by investigator-assessed PFS
- Estimate the clinical benefit of fulvestrant + AZD2014 (continuous daily schedule) relative to fulvestrant + AZD2014 (intermittent schedule), as measured by investigator-assessed PFS
- Estimate the clinical benefit of fulvestrant + AZD2014 relative to fulvestrant + everolimus or fulvestrant alone, as measured by PFS as assessed by an independent review facility [IRF]
- Assess the clinical activity, as measured by response rate (RECIST 1.1), change in tumour size at 16 weeks, clinical benefit rate, duration of clinical benefit and duration of response, of fulvestrant + AZD2014 relative to fulvestrant + everolimus or fulvestrant alone
- Establish the safety and tolerability of fulvestrant + AZD2014 relative to fulvestrant + everolimus or fulvestrant alone
- Establish the safety of the intermittent schedule of AZD2014 relative to the continuous daily schedule of AZD2014
- Estimate the overall survival benefit of fulvestrant + AZD2014 relative to fulvestrant + everolimus or fulvestrant alone
- Investigate the effects of fulvestrant +/- AZD2014 or everolimus on bone-turnover biomarkers
- Compare the differences in patient reported outcomes as measured by the Functional Assessment of Cancer Therapy-General (FACT-G) scale together with the Breast-Anti-A and Endocrine Symptom (FACTAnti-A-ES) subscales.[3]
- Investigate the pharmacokinetics of AZD2014 in breast cancer patients co-administered with fulvestrant
- Determine the minimum plasma concentration at steady state in breast cancer patients of fulvestrant alone and when administered in combination with AZD2014 or everolimus

2.4 Exploratory objectives

The exploratory objectives of this study are to:

- Estimate the clinical activity (as measured by response rate, duration of response, and CBR) of fulvestrant + AZD2014 (continuous schedule) in patients who switch to this treatment after progression on fulvestrant + everolimus
- Estimate the clinical benefit of fulvestrant + AZD2014 relative to fulvestrant + everolimus or fulvestrant alone
  - in patients with and without aberrant activation of the PI3K/Akt/mTOR pathway
  - in patients with primary or secondary endocrine resistance
- Explore potential biomarkers that may help predict response to fulvestrant + AZD2014 compared with fulvestrant + everolimus or fulvestrant alone
- Investigate the relationship between AZD2014 PK and clinical outcomes (e.g. efficacy and safety parameters)

3 STUDY DESIGN

3.1 Overview

This is an open-label, multicentre, 4-arm randomised phase II trial of fulvestrant + AZD2014 at a continuous daily schedule and fulvestrant + AZD2014 at an intermittent schedule (2 days on, 5 days off) versus fulvestrant + everolimus versus fulvestrant alone in patients with ER-positive, HER2-negative advanced or metastatic breast cancer, whose disease relapsed during treatment with (or within 12 months after discontinuation of) an AI in the adjuvant setting or progressed during treatment with an AI in the metastatic setting.

[3] Not all patients will contribute to this endpoint. Contribution will be dependent on the availability of the relevant questionnaire in the local language. Refer to section 8.1.3

The original study was designed as a 3-arm phase II trial in the same patient population, randomising patients (1:2:1) to Fulvestrant, Fulvestrant + AZD2014 or Fulvestrant + everolimus, but was amended to incorporate a 4th arm in which AZD2014 will be given at an intermittent schedule (2 days on, 5 days off). Patients recruited in the 3-arm design will be included in the analyses in this study.

Patients will be randomised (2:3:3:2) to one of the four treatment arms:

- Fulvestrant
- Fulvestrant + AZD2014 (continuous daily schedule)
- Fulvestrant + AZD2014 (intermittent schedule - 2 days on, 5 days off)
- Fulvestrant + everolimus

Randomization will be stratified by the following criteria:

- Measurable disease (vs. non-measurable).
- Sensitivity to prior endocrine therapy (sensitive versus resistant)

Sensitivity to prior endocrine therapy is defined as (i) at least 24 months of endocrine therapy before recurrence in the adjuvant setting or (ii) a complete or partial response to at least one line of prior metastatic endocrine treatment, or (iii) stabilization for at least 24 weeks of at least one line of endocrine therapy for locally advanced and/ or metstatic breast cancer.

Treatment will be continued until disease progression unless there is evidence of unacceptable toxicity, or if the patient requested to be withdrawn from the study. If one of the treatments (fulvestrant or mTOR inhibitor) is discontinued prior to disease progression, patients should be continued on single agent treatment until progression or evidence of unacceptable toxicity.

At the time of documented disease progression (using RECIST 1.1), patients randomized to receive fulvestrant + everolimus who still meet eligibility criteria (see Section 5.4. and 5.5.[4]) may be permitted to switch treatment with fulvestrant + AZD2014 (continuous schedule). Treatment switch must begin no later than 28 days after the clinic visit at which progression is determined. Patients will receive switched treatment until progression, intolerable toxicity, elective withdrawal from the study, or until the completion or termination of the study, whichever occurs first.

Tumour evaluations will be performed before the initiation of treatment, every 8 weeks during the first 40 weeks and every 12 weeks thereafter until disease progression. The study will also assess the relationship between the anticipated anti-tumour activity of the treatment regimen and biological characteristics of patients' tumour at baseline. This is summarised in Figure 3.

Detailed visit-by-visit study procedures are contained in Section 8 and Table 10 and Table 11; a treatment schedule is provided in Figure 4 and 5.

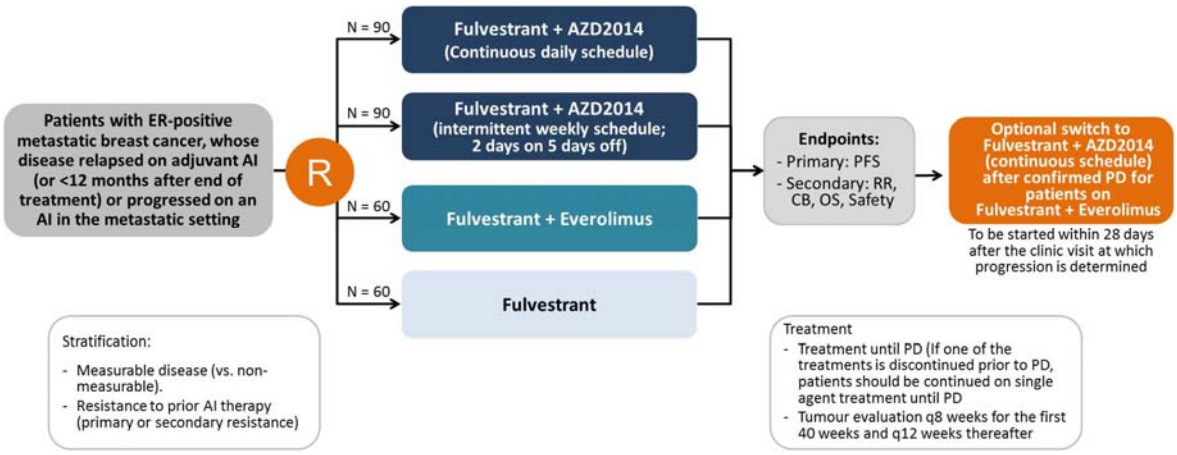

Figure 3: Overall study design

[4] With the exception of pre-treatment with everolimus and/or fulvestrant

3.2 Rationale for the study design

3.2.1 General rationale

- Resistance to endocrine therapy remains a major clinical challenge in ER-positive advanced or metastatic breast cancer
- Approximately 50% of ER-positive primary breast cancers show abnormal intrinsic activation of the PI3K/mTOR pathway (e.g. through activating mutations or amplification of the PIK3CA gene, loss of PTEN, loss of INPP4B) which has been associated with endocrine resistance
- There is increasing evidence that increased signaling (intrinsic or acquired) through the PI3K/Akt/mTOR pathway plays a critical role in endocrine resistance
- Multiple lines of preclinical investigation demonstrate that inhibition of mTOR can overcome endocrine resistance; preclinical studies suggest synthetic lethality of PI3K/Akt/mTOR inhibition and estrogen deprivation, providing a strong rationale for the combination of PI3K/Akt/mTOR pathway inhibitors and endocrine therapy

3.2.2 Rationale for the use of Fulvestrant as endocrine backbone

- Fulvestrant has established efficacy in the targeted patient population (Section 1.1)
- Synergistic activity has been demonstrated in preclinical experiments between mTOR inhibition and the effect of fulvestrant, with the combination being significantly more effective than each drug taken separately; preliminary results from clinical studies confirm antitumour efficacy of combinations of fulvestrant and everolimus, AZD2014 or PI3K inhibitors.
- The low probability of a drug-drug interaction between AZD2014 and fulvestrant or everolimus, respectively

3.2.3 Rationale for the use of everolimus

- Pre-clinical data has shown substantial synergism between everolimus and endocrine treatment in sensitive and resistant ER-positive breast cancer models both *in vitro* and *in vivo.*
- Randomised clinical trials have demonstrated a substantial benefit of adding everolimus to different classes of endocrine agents in a variety of clinical settings, especially in endocrine resistance
- Everolimus is approved for the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor.
- Although everolimus is currently not approved for this specific indication, there is the potential that the standard of care treatment in this patient group may change during the delivery of this study with everolimus becoming standard of care; this trial will therefore provide information of AZD2014 in combination with fulvestrant versus fulvestrant alone and versus fulvestrant in combination with everolimus

3.2.4 Rationale for the use of AZD2014

- There is increasing evidence that inhibition of only mTORC1 with rapalogues such as everolimus sets off a negative feedback mechanism that leads to increased AKT signalling and is linked with treatment resistance
- AZD2014 is a dual inhibitor of both mTORC1 (rapamycin-sensitive) and mTORC2 (rapamycin insensitive); compared to rapalogues, AZD2014 has a broader range of growth inhibitory activity in preclinical models based on a more profound mTORC1 inhibition and the additional inhibition of mTORC2
- AZD2014 is especially effective in ER-positive breast cancer models, showing superior activity to everolimus both in hormone-sensitive and resistant models
- Preliminary data from the ongoing phase I trials have confirmed clinical activity in MBC with in 5 patients with ER-positive disease showing partial responses (one in the monotherapy trial and 4 in combination with fulvestrant) and 7 patients having stable disease, 4 in the monotherapy trial and 3 in the Fulvestrant combination trial.

- A weekly dosing schedule with 2 days of high dose exposure of AZD2014 with a subsequent drug holiday for 5 days is being explored, because of a potential improved dose/PK/safety and PD relationship of a short high dose exposure for around 72h with a subsequent drug holiday for 4 days

3.2.5 Rationale for the use of two schedules of AZD2014

- Most preclinical and clinical applications of PI3K- or mTOR inhibitors, including AZD2014 and everolimus, use continuous daily dosing schedules and a recommended phase 2 dose of AZD2014 of 50 mg BD has been established for the continuous daily schedule. This schedule is currently being evaluated in another phase 2 study.
- Preclinical models suggest a relationship between higher exposure (AUC) of PI3K or mTOR inhibitors and greater efficacy. AZD2014 has a short half-life compared to other mTOR inhibitors, which enables high dose intermittent schedules to be tolerated. These deliver greater pathway suppression for a relatively shorter time than continuous dosing, which may improve the risk/benefit profile. An intermittent schedule of AZD2014 dosed for 2 days BD followed by 5 days of no dosing, has demonstrated a favourable toxicity profile in Phase I studies and will be further evaluated in the MANTA trial

3.2.6 Rationale for the use of Fulvestrant alone

- Despite a strong preclinical rationale and substantial benefits with other classes of endocrine agents in clinical trials, there are currently no clinical data available to demonstrate a benefit of adding everolimus to fulvestrant; consequently, fulvestrant single agent remains a standard therapeutic option and a fulvestrant alone arm is included to assess the true benefit of adding everolimus or AZD2014 in this setting; this trial will give further evidence, if estrogen receptor downregulation by Fulvestrant is equally effective to aromatase inhibition, when combined with agents targeting the mTOR pathway.

3.2.7 Justification of selecting the target population

- The trial is confined to postmenopausal women with ER-positive, HER2-negative, advanced or metastatic breast cancer whose disease relapsed during treatment with (or within 12 months after discontinuation of) an AI in the adjuvant setting or progressed during treatment with an AI in the metastatic setting, as this is the subgroup generally considered for endocrine treatment with fulvestrant.
- Patients with life-threatening metastatic visceral disease defined e.g. as extensive hepatic involvement or symptomatic pulmonary lymphangitic spread are excluded as these patients are generally better considered for chemotherapy; patients with discrete pulmonary parenchymal metastases are eligible, provided their respiratory function is not compromised as a result of disease.
- Preclinical and clinical studies suggest that PI3K wild-type or mutant tumours are equally affected by combined endocrine therapy and mTOR-inhibition, suggesting that eligibility should not be restricted by PIK3CA mutation status. Prespecified subset analyses are planned to characterize the relevance of PI3K pathway activation for the response to the study treatment.
- Patients with HER2 over-expressing tumours are excluded as these patients would generally be considered for HER2-directed therapy

3.2.8 Justification of Treatment Switch

- Currently, there are limited non-chemotherapy treatment options after second-line endocrine treatment for patients with ER-positive MBC; patients must be initially randomised to Fulvestrant + everolimus to be eligible for treatment switch.
- Mounting evidence supports the involvement of the PI3K/mTOR pathway in the development of endocrine resistance in HR-positive breast cancer and the combination of Fulvestrant and AZD2014 has demonstrated activity in preclinical models of endocrine resistance; AZD2014 has demonstrated superior activity to everolimus in preclinical models, based on a more profound mTORC1 inhibition and the additional inhibition of the mTORC2-mediated feedback activation loop, which has been associated with resistance to everolimus. AZD2014 has also demonstrated activity in everolimus resistant cell lines.

3.3 Benefit/risk and ethical assessment

3.3.1 Potential benefits

The PI3K/AKT/mTOR pathway is frequently deregulated in ER-positive advanced breast cancer and drives tumour growth and cell survival. PI3K/AKT/mTOR pathway activation is frequently associated with primary or acquired resistance to endocrine therapy and multiple lines of preclinical and clinical investigation have demonstrated that the addition of mTOR, Akt or PI3K-pathway inhibitors can significantly increase the activity of endocrine therapy and overcome resistance.

This study is investigating whether AZD2014 when combined with fulvestrant has the potential to provide benefit in terms of increased efficacy in patients with AI-refractory advanced or metastatic with or without PI3K-pathway activation, compared to treatment with fulvestrant alone or fulvestrant plus everolimus.

Everolimus is a potent rapalogue inhibitor of mTORC1 signalling, but not mTORC2. Preclinical studies have demonstrated substantial anti-tumour activity of everolimus in combination with endocrine therapy in ER-positive breast cancers and a recent randomised clinical study comparing exemestane with or without everolimus in non-steroidal aromatase inhibitor refractory ER-positive MBC demonstrated a significant PFS benefit with a HR of 0.36 (95%CI 0.27-0.47) in favour of the combination. Clinical trials with everolimus and fulvestrant at the dose level of 500 mg have not been reported and the combination is therefore currently not clinically indicated outside clinical trials, despite a strong rationale supporting this combination.

AZD2014 is a potent and highly selective mTOR kinase inhibitor targeting both mTORC1 (rapamycin-sensitive) and mTORC2 (rapamycin insensitive) complexes (IC50 < 10 nM). Non-clinical in vitro and in vivo assays have demonstrated inhibition of phosphorylation of the downstream targets of both mTORC1 (phosphorylation of pS6 at serine 235/236) and mTORC2 (phosphorylation of AKT at serine 473), tumour cell proliferation and xenograft tumour growth models. Furthermore, preclinical studies have demonstrated strong synergistic antitumour activity when AZD2014 and endocrine therapy where combined in ER-positive models. Further details of non-clinical data are available in section 1 and in the Investigators' Brochure.

In addition to the continuous daily schedule for AZD2014, this study will also investigate an intermittent weekly schedule, as data generated to date suggest that intermittent high dose schedules of AZD2014 delivering maximum target inhibition for a relatively short time may improve the risk/benefit profile.

3.3.2 Potential risks identified from clinical studies with AZD2014 or rapalogues

The potential for adverse drug reactions associated with AZD2014 are based on the adverse event profile of the class of drugs that inhibit mTORC1 (rapamycin and its analogues temsirolimus, everolimus and ridaforolimus/deferolimus) and from observations from non-clinical and preliminary unvalidated data from the ongoing AZD2014 clinical monotherapy and combination studies (D2770C00001, D2270C00005). A weekly schedule is being explored additionally in order to potentially further improve the risk benefit profile of AZD2014. Specific patient selection criteria and appropriate safety assessments, along with guidance on medical management, dose interruption and/or dose adjustments, have been incorporated into this clinical study protocol for AZD2014/everolimus. The risk is however low and a baseline CT scan of the chest is a sufficient safety measure.

3.3.2.1 Clinical safety experience with everolimus and other rapamycin analogues

In clinical studies of rapamycin and its analogues, dose-limiting toxicities consisted of mucositis, fatigue, cutaneous events, and thrombocytopenia. mTOR is involved in the regulation of glucose metabolism and glucose intolerance has been observed in 4%-13% of patients receiving rapamycin or its analogues [47,48,46,45,49]; such events are manageable in the clinic. Additionally, increases in triglycerides and cholesterol have been reported [50,51]. Pulmonary toxicity in the form of a non-infectious pneumonitis and changes in DLco have been observed with mTOR inhibitors with reversible symptoms ranging from clinically asymptomatic with radiological findings (diffuse interstitial disease, ground-glass opacities) and changes in pulmonary function tests (diffusion lung capacity for carbon monoxide decrease) to dyspnoea on exertion, dry cough and chest pain.

The most frequent grade 3-4 adverse reactions with other mTOR inhibitors in breast cancer patients (incidence ≥2% in at least one phase III study) were anaemia, fatigue, diarrhoea, infections, stomatitis, hyperglycaemia, thrombocytopenia, lymphopenia, neutropenia, hypophosphataemia, hypercholesterol-aemia, diabetes mellitus, and pneumonitis.

Everolimus: Three randomised, double-blind, placebo controlled phase III studies contribute to the safety profile of everolimus as detailed in the SPC [52]. The respective exposure in the phase III studies was:

- BOLERO-2 (CRAD001Y2301): everolimus in combination with exemestane in the treatment of

postmenopausal women with oestrogen receptor-positive, locally advanced or metastatic breast cancer who were previously treated with either letrozole or anastrozole. In total, 191 (40%) patients were exposed to everolimus therapy for ≥32 weeks. The rates of adverse reactions resulting in permanent discontinuation were 21% and 3% for the everolimus plus exemestane and the placebo plus exemestane treatment groups, respectively.

- RADIANT-3 (CRAD001C2324): everolimus plus best supportive care in patients with advanced neuroendocrine tumours of pancreatic origin. In total, 63 (31%) patients were exposed to everolimus 10 mg/day for ≥52 weeks. The rates of adverse reactions resulting in permanent discontinuation were 14% and 2% for the everolimus and placebo treatment groups, respectively.
- RECORD-1 (CRAD001C2240): everolimus plus best supportive care in patients with metastatic renal cell carcinoma. In total, 165 patients were exposed to everolimus 10mg/day for ≥4 months. The rates of adverse reactions resulting in permanent discontinuation were 7% and 0% for the everolimus and placebo treatment groups, respectively. Most adverse reactions were grade 1 or 2 in severity.

The most frequent grade 3-4 adverse reactions (incidence ≥2% in at least one phase III study) were anaemia, fatigue, diarrhoea, infections, stomatitis, hyperglycaemia, thrombocytopenia, lymphopenia, neutropenia, hypophosphataemia, hypercholesterolaemia, diabetes mellitus, and pneumonitis [52].

System	Frequency		
	Very Common	Common	Uncommon
Infections	Infections [a]	-	-
Blood and lymphatic system disorders	Anaemia, thrombocytopenia	Leukopenia, lymphopenia, neutropenia	Pure red cell aplasia
Metabolism and nutrition disorders	Hyperglycaemia, hypercholesterolaemia, hypertriglyceridaemia, anorexia	Diabetes mellitus, hypophosphate-aemia, hypokalaemia, hyperlipidaemia, hypocalcaemia, dehydration	-
Psychiatric disorders	-	Insomnia	-
Nervous system disorders	Dysgeusia, headache	-	Ageusia
Eye disorders	-	Conjunctivitis, eyelid oedema	-
Cardiac disorders	-	-	Congestive cardiac failure
Vascular disorders	-	Hypertension, haemorrhage [b]	Flushing, deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	Pneumonitis[c], dyspnoea, epistaxis, cough	Pulmonary embolism, haemoptysis	Acute respiratory distress syndrome
Gastrointestinal disorders	Stomatitis [d], diarrhoea, mucosal inflammation, vomiting, nausea	Dry mouth, abdominal pain, oral pain, dysphagia, dyspepsia	-
Hepatobiliary disorders	-	ALT increased, AST increased	-
Skin and subcutaneous tissue disorders	Rash, dry skin, pruritus, nail disorder	Palmar-plantar erythrodysaesthesia syndrome, erythema, skin exfoliation, acneiform dermatitis, onychoclasis, skin lesion, mild alopecia	Angioedema
Musculoskeletal and connective tissue disorders	-	Arthralgia	-
Renal and urinary disorders	-	Creatinine increased, renal failure (including acute renal failure)*, proteinuria*	-
General disorders and administration site conditions	Fatigue, asthenia, peripheral oedema, pyrexia, weight decreased	Chest pain	Impaired wound healing

Table 1: Tabulated summary of adverse reactions as listed in the everolimus SPC

Table 1 shows the incidence of adverse reactions reported for patients receiving everolimus 10 mg/day in at least one of the pivotal studies [52]. All terms included are based on the highest frequency reported in a pivotal study. Adverse reactions are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

[a] Includes all reactions within the 'infections and infestations' system organ class (such as pneumonia, sepsis, and isolated cases of opportunistic infections [e.g. aspergillosis, candidiasis and hepatitis B]

[b] Includes different bleeding events not listed individually

[c] Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar haemorrhage, pulmonary toxicity, and alveolitis

[d] Includes stomatitis and aphthous stomatitis, and mouth and tongue ulceration

The clinical trial that represents best the patient population treated in this study is the BOLERO-2 study. The BOLERO-2 trial evaluated the combination of everolimus (10 mg OD) and exemestane (25 mg OD) with single-agent exemestane (25 mg OD) in ER-positive, HER2-negative MBC patients whose disease was refractory to prior

treatment with letrozole or anastrozole. In this study, the freuqency of serious adverse events (as defined in the protocol) potentially attributed to study treatment was higher in the combination-therapy group (11%) as compared to exemestane alone (1%). A higher percentage of patients discontinued everolimus in the combination-therapy group than discontinued placebo in the control group because of adverse events (19% vs. 4%) and withdrawal of consent (5% vs. 2%). The most common grade 3 or 4 adverse events in the combination group were stomatitis (8%), anemia (6%), dyspnea (4%), hyperglycemia (4%), fatigue (4%), and pneumonitis (3%). Despite these differences in the safety profile, the time to deterioration of ECOG performance status and time to deterioration of quality of life (≥5%) were not statistically different between the two treatment groups. There are however few data providing information regarding burden of toxicities recorded by patients using standardised and validated symptom checklists. It is well known that clinician-reported AEs both in terms of frequency and severity show a lack of concordance with those collected via PRO measures.

Adverse Event	**Everolimus and Exemestane (N = 482)**			**Placebo and Exemestane (N = 238)**		
	Any Event (%)	Grade 3 event (%)	Grade 4 event (%)	Any Event (%)	Grade 3 event (%)	Grade 4 event (%)
Stomatitis	56	8	0	11	1	0
Rash	36	1	0	6	0	0
Fatigue	33	3	<1	26	1	0
Diarrhea	30	2	<1	16	1	0
Decreased appetite	29	1	0	10	0	0
Nausea	27	<1	<1	27	1	0
Cough	22	1	0	11	0	0
Dysgeusia	21	<1	0	5	0	0
Headache	19	<1	0	13	0	0
Decreased weight	19	1	0	5	0	0
Dyspnea	18	4	0	9	1	<1
Arthralgia	16	1	0	16	0	0
Anemia	16	5	1	4	<1	<1
Epistaxis	15	0	0	1	0	0
Vomiting	14	<1	<1	11	<1	0
Peripheral edema	14	1	0	6	<1	0
Pyrexia	14	<1	0	6	<1	0
AST level increased	13	3	<1	6	1	0
Constipation	13	<1	0	11	<1	0
Hyperglycemia	13	4	<1	2	<1	0
Pneumonitis	12	3	0	0	0	0
Thrombocytopenia	12	2	1	<1	0	<1
Asthenia	12	2	0	3	0	0
ALT level increased	11	3	<1	3	2	0
Pruritus	11	<1	0	3	0	0
Insomnia	11	<1	0	8	0	0
Back pain	11	0	0	8	1	0

Table 2: Adverse Events Irrespective of Relationship to Study Treatment (with ≥10% Incidence in the combination group) [45].

3.3.2.2 Preclinical and clinical safety experience with AZD2014

Relevant findings based on non-clinical studies or preliminary observations in completed and ongoing studies of AZD2014 in patients with advanced cancer (D2270C00001) and breast cancer in combination with Fulvestrant (D2270C00005) are summarised below.

Safety, Monotherapy *Fatigue or lethargy:* Events of fatigue or lethargy have occurred commonly in patients receiving multiple doses of AZD2014. Fatigue was amongst the most common AEs reported with a single dose of AZD2014, and at doses of 70 mg BD and 100 mg BD monotherapy was amongst those events considered as dose limiting. The medical/scientific literature reports an association with other mTOR inhibitors and lethargy or fatigue [53,54]. Furthermore, fatigue is reported amongst most common side effects for several Dual-kinase PI3K-mTOR inhibitors (GDC-0980, NVP-BEZ235, XL765). There were no pre-clinical behavioural changes suggestive of fatigue or lethargy in a rat single oral dose CNS safety pharmacology study or in rats and dogs dosed orally with AZD2014 for up to 1 month. At non-tolerated doses in mice, i.p. administration of AZD2014 was associated with hypoactivity, lack of grooming and a reduction in locomotor parameters. However, any relationship of these changes to the clinical occurrence of CTCAE grade 3 fatigue is unknown.

Gastrointestinal events: Gastrointestinal adverse events with AZD2014 were reported in rats and dogs, and included weight loss and reduced food consumption, effects on gastric emptying and intestinal transit times in rats and mucosal inflammation in dogs. Events of decreased appetite or weight loss (CTCAE grade 1 or 2) have been reported commonly in patients receiving AZD2014 as monotherapy. Events of nausea and vomiting and mucosal inflammation/stomatitis have also occurred commonly in patients receiving AZD2014 as monotherapy. CTCAE grade 3 stomatitis has been reported in a small number of patients who received AZD2014 at a dose of 70 mg BD, which resolved on dose reduction or stopping treatment. CTCAE grade 1 or 2 nausea and vomiting were reported intermittently throughout all dose levels in some patients, with one CTCAE grade 3 (serious adverse event) in one patient at 50 mg BD. Diarrhoea (CTCAE grade 1) has commonly been reported in patients receiving AZD2014.

Skin-type events: There have been reports of events of rash of any typein patients receiving AZD2014. The majority had CTCAE grade 1 rash, however CTCAE grade 2 and 3 rash was reported in some patients. There was no clear pattern in the type of rash reported which included erythematous, maculopapular and pruritic. Patients will be monitored for dermatological adverse events; if an event is non-tolerable, dose holidays and/or reductions are recommended to manage the intensity of rash, allowing continued dosing on study once symptoms have improved and/or cortisol cream applications can be considered.

Glucose homeostasis: Non clinical studies of AZD2014 in rats and dogs indicated reversible elevations in plasma glucose and/or insulin. Histopathological changes occurred in 2 dogs after dosing for up to 14 days: pancreatic islet cell hypertrophy, hepatocyte glycogen vacuolation; and in rats after 3 months of dosing: increased liver glycogen. Insulin and blood glucose elevations have been observed in both monotherapy and in combination therapy studies, a finding frequently described with other mTOR inhibitors as well. Hyperglycaemia has been reported in patients receiving AZD2014. There have been reports of SAEs of hyperglycaemia reported with AZD2014, including patients requiring inpatient hospitalisation and treatment with insulin to achieve glycaemic control.

Respiratory effects: Transient changes in respiratory parameters (increase in inspiratory flow, respiratory rate and minute volume with decreases in inspiration time and tidal volume) occurred in a respiratory safety pharmacology study in rats following single oral doses of AZD2014. No treatment related lung changes were seen following dosing for up to 28 days in rats and dogs. As pneumonitis is reported as a possible class effect of mTOR inhibitors with an incidence of 5%-36%, appropriate monitoring of patients has been put in place for all studies. In study D2270C00001, 2/135 patients had AEs of pneumonitis that were related to treatment. In study D2270C00005, 3/76 patients had pneumonitis that was related to treatment. In both studies cases of cough and dyspnoea were reported.

Cardiovascular effects: In pre-clinical safety pharmacology studies, increases in heart rate, blood pressure, myocardial contractility, coronary flow and minor QTc prolongation were observed. 9 patients out of 135 who received at least 1 dose of AZD2014 in study D2270C00001 had significant repolarisation abnormalities. Primary cardiac repolarisation abnormalities, T-wave inversion, were observed on ECGs in 4 of the first 54 patients treated with AZD2014 in study D2270C00001 progressing to T-wave inversion in 3 of those patients who continued on treatment. These changes returned back to low/normal over a period of weeks while on treatment. The patients with these findings showed no clinical signs and symptoms of compromised cardiac function or any elevations in cardiac enzymes. There were no significant QRS morphology changes during the trial. In study D2270C00001, no patient had corrected QTc using Fridericia's formula (QTcF) >500 ms. Only 3 patients had a post baseline QTcF value >470 ms. All 3 patients had transient/ intermittent CTCAE grade 1 QTcF changes, which are not considered clinically significant, and resolved while on treatment. No relevant cardiac AEs (arrhythmia) were reported in these

3 patients. In addition, 3 different patients had AEs of ECG QT prolonged reported as they had transient QTcB elevations >450 ms during the study that resolved while on treatment. All these patients had QTcF <470 ms during the study.

Haematological effects: Changes in bone marrow (hypocellularity/ decreased haematopoiesis and/or increases in adipose tissue within the bone marrow) and secondary lymphoid tissues (hypocellularity/ decreased haematopoiesis and/or lymphocytolysis in thymus, spleen, lymph nodes and/or GI tract) were seen in rats and dogs following dosing for up to 3 months or 1 month respectively. Associated changes in peripheral haematology parameters (notably reductions in lymphocytes, neutrophils and/or reticulocyte counts) were also seen. All changes showed evidence of reversibility. During the phase 1 clinical study, occurrences of mild anaemia, mainly CTC grade 1 were observed. There was 1 SAE of febrile neutropenia which was considered by the investigator to be related to AZD2014.
Renal effects: AZD2014 caused reversible changes in several urinary parameters in rats (increases in urine volume, glucose, electrolytes; decreases in pH and total protein) following single or repeat dosing, which were suggestive of possible effects on renal function. Creatinine clearance was not affected. No renal histopathological changes have been observed in any rat or dog study with AZD2014. No clinically significant renal findings were reported at any dose of AZD2014.

Genotoxicity: AZD2014 has been shown to be non-genotoxic in a battery of genetic toxicity assays.

Phototoxicity: AZD2014 had positive effects in the *in vitro* 3T3 neutral red uptake phototoxicity test. There have been no relevant clinical findings, however, based on the potential for phototoxicity, patients should be advised of the need for sunlight protection measures during administration of AZD2014, and should be advised to adopt such measures for a period of 3 months after receiving their final dose of AZD2014. Patients receiving AZD2014 will be advised to avoid excessive sun exposure and use adequate sunscreen protection if sun exposure is anticipated. Use of sunbeds/tanning booths should be avoided.

Reproductive organs: Degeneration and atrophy of the testes was observed in non-clinical studies folloiwng 1 month of dosing in dogs. Atrophy of the uterus and vagina were noted following 3 months of dosing in the rat. There have been no relevant clinical findings to date.

Safety, Phase I combination (D2270C00005):

Preliminary unvalidated data suggest, that the overall safety profile of AZD2014 in combination with Fulvestrant is broadly similar to the known individual safety profile of AZD2014 monotherapy.

Potential for Drug-drug interactions:
CYP450 induction/inhibition: CYP3A5 and CYP3A4 were identified *in vitro* as the principal P450s responsible for human metabolism of AZD2014, indicating the possibility of drug-drug interactions with inhibitors and inducers of these enzymes. Co-administration of CYP3A4 or CYP3A5 inhibitors may increase exposure to AZD2014 and hence potentially affect efficacy/toxicity and hence increase the risk of time dependent inhibition (and resultant toxicity of CYP3A4 substrates). In addition, co-administration of CYP3A4 or CYP3A5 inducers may decrease the exposure to AZD2014 and hence potentially affect efficacy. AZD2014 showed no time dependent inhibition of CYPs, and only weak reversible inhibition of CYPs 2C8 (IC50 ≈ 21μM).
AZD2014 has also been identified in vitro as a substrate for the drug transporters Pgp (MDR1) and BCRP. Co-administration of CYP3A4, CYP3A5, CYP2C8, Pgp (MDR1) or BCRP inhibitors may increase exposure to AZD2014 and increase the likelihood of toxicity. In addition, co-administration of CYP3A4, CYP3A5, Pgp (MDR1) or BCRP inducers may decrease the exposure to AZD2014 and hence potentially affect efficacy. Co-administration of AZD2014, particularly at high doses, with known or possible substrates of these enzymes / transporters may lead to their increased exposure and requires careful evaluation.

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of P-Glycoprotein (PgP). Therefore, absorption and subsequent elimination of everolimus may be influenced by products that affect CYP3A4 and/or PgP. *In vitro*, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6. Substances that are inhibitors of CYP3A4 or PgP may therefore increase everolimus blood concentrations by decreasing metabolism or the efflux of everolimus from intestinal cells. Substances that are inducers of CYP3A4 or PgP may decrease everolimus blood concentrations by increasing metabolism or the efflux of everolimus from intestinal cells.
The following restrictions will therefore be put in place in the study (please refer to Appendix 2 of this clinical study protocol for listings of relevant drugs): All patients should avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to moderately or potently modulate CYP3A4, CYP3A5 or CYP2C8 enzyme activity from the time they enter the screening period until 2 weeks after the last dose of treatment, ensuring no study treatment is started until the appropriate wash-out period for each drug is reached (refer to Appendix 2). Short term administration of such drugs may be permitted, although concomitant use could lead to lower plasma levels of AZD2014 and everolimus and a potential reduction in clinical efficacy. If co-administration is necessary then

additional monitoring for signs of toxicity related to increased exposure to the substrates is required. All patients should avoid concomitant use of sensitive or narrow therapeutic range substrates of the drug metabolizing enzymes CYP2C8, CYP2C9, CYP2C19, CYP2D6 or the drug transporters Pgp (MDR1), BCRP, OATP1B1, OATP1B3, OCT1 and OCT2, from the time they enter the screening period until 2 weeks after the last dose of treatment, ensuring no study treatment is started until the wash-out period appropriate for each drug has elapsed (refer to Appendix 2). Short term administration of substrates of CYP2C8, CYP2C9, CYP2C19, CYP2D6, Pgp (MDR1), BCRP, OATP1B1, OATP1B3, OCT1 and OCT2 enzymes / transporters may be permitted but for known or potential sensitive or narrow therapeutic range substrates (see Appendix 2) the study drug should be withheld for 3 days prior to the first dose and not restarted until the concomitant therapy has been discontinued and the appropriate washout period elapsed. An increased frequency of monitoring of anticoagulation during treatment with AZD2014/everolimus is advised in patients who receive regular anticoagulant therapy; such patients should stop medication with AZD2014/everolimus if they experience CTCAE grade 3 thrombocytopenia.

3.3.3 Safety plan

Eligibility criteria for this study were selected to enhance the safety of patients in this trial. A number of exclusion criteria are specifically based on the known safety profiles of the study drug treatments (see below), including the known safety profile of everolimus, as well as nonclinical and clinical data for AZD2014. The complete list and description of eligibility criteria for this study are provided below.

Glucose homeostasis: In order to reduce the potential risk of exacerbating abnormal glucose profiles, patients with Type I or patients with poorly controlled Type II diabetes mellitus (defined as glycosyated haemoglobin (HbA1c) ≥8% at screening) will be excluded from this clinical study. Glucose profiles will be performed on the first day of each cycle and on discontinuation of AZD2014/everolimus.

In addition, because of the pharmacological activity of AZD2014 on glycolysis and insulin signalling, fasting lipid profiles (triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL) and cholesterol) will also be monitored at baseline, weeks 8, 16, 24 and every 12 weeks thereafter and at discontinuation of AZD2014 or everolimus. Guidelines for the managment of hyperglycaemia are provided in section 7.6.2.3. of this protocol to aid investigator management of elevated blood glucose.

Stomatitis/Oral mucositis: There are no standard exclusion criteria for stomatitis. Stomatitis can be managed with interruptions and potentially dose reduction to AZD2014 or everolimus dosing. Patient reports of stomatitis are expected to be evaluated and treated by investigators according to local practice (eg, use of non alcoholic salt water mouth wash, topical analgesic mouth treatments with or without topical corticosteroids). Guidelines for the management of stomatitis will be provided in section 7.6.2.5 of this protocol.

Diarrhoea: There are no standard exclusion criteria for patients with diarrhoea. Diarrhoea can be managed with treatment and interruptions to AZD2014 or everolimus dosing. Patient reports of diarrhoea are expected to be evaluated and treated by investigators according to local practice (eg, use of medications such as loperamide, need for IV fluid replacement). Guidelines for the management of diarrhoea will be provided in section 7.6.2.6. of this protocol.

Respiratory: As non-infectious pneumonitis and changes in DLco have been observed in patients treated with AZD2014 and everolimus, patients with clinically significant pulmonary dysfunction are excluded from the trial. Patients should be monitored carefully (including physical examinations and periodic CT scans) for changes of pulmonary status during treatment. DLco and CT scans may be used to confirm and evaluate changes in pulmonary status if clinically indicated.

Patients experiencing symptomatic or asymptomatic pneumonitis should be treated per standard of care and guidelines in Section 7.6.2.8. Use of corticosteroids should be considered for symptomatic cases of non-infectious pneumonitis.

Rash: There are no standard exclusion criteria for patients with rash. Rash can be managed with treatment and interruptions to AZD2014 and everolimus dosing. Patient reports of rash are expected to be evaluated and treated by investigators according to local practice (eg, use of oral or topical steroids, use of oral antihistamine). Guidelines for the management of rash will be provided in section 7.6.2.7 of this protocol.

Cardiovascular effects: Standard exclusion criteria for unstable cardiac conditions, risk factors for QT prolongation, or laboratory parameters that may affect cardiac parameters, are detailed in Section 5.5. Additional clarification is provided to exclude patients who have experienced coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, angina pectoris, congestive heart failure New York Heart Association (NYHA) ≥Grade 2 within the last 12 months; patients with an abnormal echocardiogram at baseline (LVEF below 50%) are also excluded. Regular monitoring of vital signs and ECG parameters will be conducted during treatment with AZD2014 and everolimus.

Haematopoietic system: Patients with inadequate bone marrow reserve as demonstrated by any of the following laboratory values (absolute neutrophil count <1.5 x 10^9/L; platelet count <100 x 10^9/L) will be excluded from the study. Haematological parameters (including leucocytes, neutrophils, haemoglobin and platelets) will be monitored as part of the standard laboratory safety assessment.

Liver and pancreas: In order to reduce the potential risk of acute liver necrosis, patients with evidence of severe or uncontrolled systemic liver disease including severe hepatic impairment, or abnormal liver enzymes at screening (AST or ALT >2.5x ULN or total bilirubin >1.5x ULN in the absence of liver metastases) are excluded from participating in the study. During the study, liver function tests will be monitored as part of the standard laboratory safety assessment. An algorithm will be provided separately to this protocol to provide guidance for the investigation and management of patient reported symptoms of potential acute liver dysfunction and any liver transaminase results in excess of 8x ULN occurring at any time during the study. This algorithm should be used in conjunction with the FDA Draft Guidance for the evaluation of Drug Induced Liver Injury (FDA 2009).

All enrolled patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, and laboratory measurements. Patients will be evaluated for adverse events (all grades), serious adverse events, and any adverse events requiring drug interruption or discontinuation throughout the course of the study. Any outcomes of these pre-specified early safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification to the appropriate ECs.

Two committees will be convened to evaluate the safety of this trial, the trial steering committee (TSC) and the independent data monitoring committee (IDMC). The role of the TSC is to provide overall supervision of the trial and ensure that it is conducted in accordance with GCP and the Protocol. The TSC will review the recommendations of the IDMC and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. The role of the IDMC is to provide independent advice on data and safety aspects of the trial. The data will be reviewed (approximately 12 monthly) by an IDMC, consisting of at least two clinicians not entering patients into the trial and an independent statistician. The IDMC will be asked to recommend whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. If a decision is made to continue, the IDMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC.

3.3.4 Overall benefit-risk and ethical assessment

Although there can be no certainty of clinical benefit to patients, non-clinical data with AZD2014 and other mTOR inhibitors and clinical data with everolimus support the hypothesis that mTOR inhibition is a valid target for ER-positive MBC with or without PIK3CA mutations. Inhibition of mTOR in a similar indication but with different endocrine treatment has led to substantial and meaningful benefits in PFS in previous studies. The non-clinical safety profile and emerging clinical profile from the early clinical studies have not identified risks that would preclude investigation in this setting. This is the first phase 2 study in which AZD2014 will be administered to breast cancer patients in combination with endocrine therapy, with the exception of a phase I study of fulvestrant and AZD2014.

Nonclinical and Phase Ia data for AZD2014 and everolimus have identified no relevant overlap with the well-defined safety profile of fulvestrant. The current experience with AZD2014 in cancer patients also confirms that AZD2014 can be given safely and is associated with an acceptable toxicity profile. However, AZD2014 remains an experimental agent and additional side effects might be described at later stages. Most studies to date included heavily pre-treated patients with advanced or metastatic cancers. The majority of adverse effects in these studies were grade 1 or 2 and were generally rapidly reversible. The incidence of moderate or severe toxicities was low and appears comparable with what has been observed with allosteric mTOR inibitors such as everolimus.

In addition to the continuous daily schedule for AZD2014, this study will also investigate an intermittent weekly schedule to see whether there is the potential of a further improved risk/benefit profile with a short high dose dosing period of 2 days BID dosing per week. Preliminary data for the intermittent weekly schedule have demonstrated a safety profile that appears at least comparable if not favourable to continuous daily dosing.

The study design aims to minimise potential risks. Eligibility criteria were selected to enhance the safety of patients in this trial and a number of exclusion criteria are specifically based on the known safety profiles of the study drug treatments. A dose modification strategy for management of toxicity and monitoring is in place for those risks deemed to be most likely or serious.

Thus the benefit/risk assessment for this study supports the co-administration of AZD2014 with fulvestrant in patients with advanced or MBC with or without activation of the PIK3CA pathway.

4 ENDPOINTS

4.1 Primary Efficacy Outcome Measure

The primary outcome measure for this study is:

- Progression-free survival (PFS), defined as the time from the date of randomisation to the date of first documented tumour progression based on investigator assessment (using RECIST 1.1) or death from any cause, whichever occurs first.

4.2 Secondary Efficacy Outcome Measures

The secondary outcome measures for this study are:

- Progression-free survival, defined as the time from the date of randomisation to the date of first documented tumour progression as assessed by an independent review facility [IRF] (using RECIST 1.1) or death from any cause, whichever occurs first.
- Objective response, defined as a complete or partial response, based on investigator and IRF assessment using RECIST 1.1
- Average change (%) in tumour size at 16 weeks compared to baseline, based on investigator and IRF assessment using RECIST 1.1; tumour size is defined as the sum of the longest diameters of the target (i.e. measurable tumour) lesions
- Clinical Benefit (CB), defined as number of patients with complete or partial response or stable disease maintained ≥24 weeks, based on investigator and IRF assessment using RECIST 1.1)
- Overall survival, defined as the time from date of randomisation to the date of death due to any cause
- Duration of response, defined as the time from first documentation of complete or partial response to disease progression based on investigator and IRF assessment using RECIST 1.1
- Duration of clinical benefit, defined as the time from randomisation to disease progression based on investigator and IRF assessment using RECIST1.1 in patients with CB
- Percentage change in serum of serum beta C-terminal cross-linking telopeptide of Type I collagen (βCTx) and N-terminal propeptide of Type I procollagen (PINP) from screening/baseline to each time that samples are collected.
- Patient reported outcomes, as assessed by the Functional Assessment of Cancer Therapy-General (FACT-G) scale together with the Breast-Anti-A and Endocrine Symptom (Anti-A-ES) subscales.[5]

4.3 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence of serious adverse events
- Incidence of grade 3 and 4 adverse events (CTCAE, version 4.03)
- Incidence of all adverse events of all grades
- Incidence of the following selected adverse events (any grade)
  - Hyperglycaemia
  - Diarrhoea

[5] Not all patients will contribute to this endpoint. Contribution will be dependent on the availability of the relevant questionnaire in the local language. Refer to section 8.1.3

  - Stomatitis
  - Rash
  - Interstitial pneumonitis
  - Fatigue
  - T- wave changes
- Adverse events leading to discontinuation of the study medication
- Changes in vital signs and clinical laboratory results during and following study drug administration

4.4 Pharmacokinetics Outcome Measures

The PK outcome measures for this study are as follows:

- Plasma drug clearance (CL/F), estimated maximum drug concentration (C_{max}), elimination half-life ($t_{1/2}$) and volume of distribution (Vss/F) for AZD2014
- Css_{min} for fulvestrant

4.5 Exploratory Outcome Measures

- Alterations in DNA and RNA, including mutational status, RNA expression levels, DNA copy number, and protein expression

5 PATIENT SELECTION AND ELIGIBILITY TARGET POPULATION

The target population for this trial is patients with ER-positive, HER2-negative advanced or metastatic breast cancer, .whose disease relapsed during treatment with (or within 12 months after discontinuation of) an AI in the adjuvant setting or progressed during treatment with an AI in the metastatic setting. Specific inclusion and exclusion criteria are detailed below.

5.1 Source of patients

Postmenopausal women with ER-positive advanced or metastatic breast cancer will be recruited from breast cancer clinics within participating centres.

5.2 Number of patients

The planned sample size for the four arm component of the study is 300 patients with 90 patients each in the two fulvestrant + AZD2014 groups and 60 patients each in the fulvestrant alone and the fulvestrant + everolimus groups, respectively. Therefore the total sample size will be slightly greater than 300, as some patients will already have been recruited into the first part of the study (i.e. prior to the addition of the AZD2014 intermittent schedule) and these patients will be included in the final analyses.

5.3 Inclusion Criteria

Each patient must meet **all of the following inclusion criteria** to be enrolled in the study:

1. Written informed consent prior to admission to this study
2. Women, age ≥18 years
3. Histologically confirmed breast cancer
4. Metastatic and/ or locally recurrent disease; locally recurrent disease must not be amenable to resection with curative intent (patients who are considered suitable for surgical or ablative techniques following potential down-staging with study treatment are not eligible).
5. Patients must have:
   a. at least one lesion, not previously irradiated, that can be measured accurately at baseline as ≥ 10mm in the longest diameter (except lymph nodes which must have short axis ≥ 15mm) with computed tomography (CT) or magnetic resonance imaging (MRI) which is suitable for accurate repeated measurements, or

   b. lytic or mixed (lytic + sclerotic) bone lesions in the absence of measurable disease as defined above; patients with sclerotic/osteoblastic bone lesions only in the absence of measurable disease are not eligible

6. Radiological or clinical evidence of recurrence or progression
7. ER-positive disease[6], defined as tumour cells being positive for ER with ≥ 1% of tumour cells positive for ER on IHC or IHC score (Allred) of ≥ 3
8. HER2-negative disease[1] with 0, 1+ or 2+ intensity on IHC and no evidence of amplification on ISH.
9. Formalin fixed, paraffin embedded tumour sample from the primary and/or recurrent cancer must be available for central testing
10. Postmenopausal women. Women will be considered postmenopausal if they meet one of the following criteria:
    a. Age ≥ 50 years and 1 year or more of amenorrhea
    b. Age < 50 years and 1 year or more of amenorrhea, with an estradiol assay < 20pg/mL
    c. Age < 50 with prior hysterectomy but intact ovaries with an estradiol assay < 20pg/mL
    d. Status after bilateral oophorectomy (≥ 28 days prior to first study treatment)

    Note: Ovarian radiation or treatment with a luteinizing hormone-releasing hormone (LHRH) agonist (goserelin acetate or leuprolide acetate) is not permitted for induction of ovarian suppression.
11. Disease refractory to aromatase inhibitors (AI), defined as
    a. Disease recurrence while on, or within 12 months of end of adjuvant treatment with letrozole, anastrozole, or exemestane, or,
    b. Progression while on, or within one month of end of letrozole, anastrozole or exemestane treatment for locally advanced or metastatic Breast Cancer.

    Note: Any number of lines of hormonal therapy before or after AI therapy is allowed.

    Note: Letrozole, anastrozole or exemestane do not have to be the last treatment prior to randomisation.
12. Haematologic and biochemical indices within the ranges shown below. These measurements must be performed within one week prior to randomisation
    a. ANC ≥ 1500 cells/µl, haemoglobin ≥ 9g/dl, and platelet count ≥ 100000/µl.
    b. Serum Creatinine < 1.5 times ULN or > 1.5 times ULN concurrent with creatinine clearance ≥ 50ml/min (measured or calculated by Cockcroft and Gault equation), confirmation of creatinine clearance is only required when creatinine is > 1.5 times ULN.
    c. Bilirubin level < 1.5 x ULN if no demonstrable liver metastases or < 3 times ULN in the presence of liver metastases.
    d. AST or ALT < 2.5 x ULN.
    e. International normalized ratio (INR) < 1.5 and activated partial thromboplastin time (aPTT) < 1.5 x ULN; for patients requiring therapeutic anticoagulation therapy, a stable INR ≤ 2.5 x ULN is required to mitigate potential bleeding.
    f. No clinically relevant and treatment resistant abnormalities in potassium, sodium, calcium (corrected for plasma albumin) or magnesium.
    g. Fasting serum cholesterol ≤ 300 mg/dl or 7.75 mmol/L and fasting triglycerides ≤ 2.5 ×ULN. In case one or both of these thresholds are exceeded, the patient can only be included after initiation of statin therapy and when the above mentioned values have been achieved.
13. ECOG performance status 0-2
14. Non-childbearing potential (i.e., physiologically incapable of becoming pregnant), including any female who has had a hysterectomy, bilateral oopheroctemy, bilateral tubular ligation or is post-menopausal (total cessation of menses for ≥ 1 year)

5.4 Exclusion Criteria

Patients meeting **any of the following exclusion criteria** are not to be enrolled in the study.

1. Presence of life-threatening metastatic visceral disease, defined as extensive hepatic involvement or any

[6] The ER positive /HER2 negative status applies to the last histology taken, whether this was in the primary or advanced setting.

degree of brain or leptomeningeal involvement (past or present), or symptomatic pulmonary lymphangitic spread. Patients with discrete pulmonary parenchymal metastases are eligible, provided their respiratory function is not compromised as a result of disease.

2. More than one line of prior chemotherapy for metastatic breast cancer

   Note: A chemotherapy line in advanced disease is an anticancer regimen(s) that contains at least 1 cytotoxic chemotherapy agent and given for 21 days or longer. If a cytotoxic chemotherapy regimen was discontinued for a reason other than disease progression and lasted less than 21 days, then this regimen does not count as a "prior line of chemotherapy"
3. Prior chemotherapy, biological therapy, androgens, thalidomide, immunotherapy, other anticancer agents or any investigational agents within 14 days of starting study treatment (not including palliative radiotherapy at focal sites), radiotherapy with a wide field of radiation (greater than or equal to 30% marrow or whole pelvis or spine) within 4 weeks of starting study treatment, or strontium-90 (or other radiopharmaceuticals) within the past 3 months or major surgery within 4 weeks prior to entry into the study (excluding the placement of vascular access); with the exception of alopecia, all unresolved toxicities from prior treatment should be no greater than CTCAE grade 1 at the time of starting study treatment
4. Prior treatment with fulvestrant or everolimus
5. Prior treatment with PI3K inhibitors, Akt inhibitors or other mTOR inhibitors.
6. Patients receiving concomitant immunosuppressive agents or chronic systemic corticosteroids (≥10 mg prednisolone or an equivalent dose of other anti-inflammatory corticosteroids) use for ≥28 days at the time of study entry except in cases outlined below: Topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g. intra-articular) are allowed. Patients on stable low dose of corticosteroids for at least two weeks before randomisation are allowed
7. Current refractory nausea and vomiting, chronic gastrointestinal disease or inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of the study medication
8. Clinically significant pulmonary dysfunction
9. Significant cardiovascular disease; patients who have experienced any of the following procedures or conditions currently or in the preceding 12 months are excluded:
   a. History of myocardial infarction, acute coronary syndromes (including unstable angina), or history of coronary angioplasty/stenting/bypass grafting.
   b. History of symptomatic congestive heart failure (CHF) New York Heart Association (NYHA) Classes II-IV or LVEF <50% by either ECHO or MUGA
   c. Severe cardiac arrhythmia requiring medication or severe conduction abnormalities
   d. Poorly controlled hypertension (resting diastolic blood pressure >100 mmHg)
   e. Clinically significant valvular disease, cardiomegaly, ventricular hypertrophy, or cardiomyopathy
10. QTc prolongation defined as a QTc interval >470 msecs or other significant ECG abnormalities including 2nd degree (type II) or 3rd degree AV block or bradycardia (ventricular rate <50 beats/min)
11. Concomitant medications known to prolong QT interval, or with factors that increase the risk of QTc prolongation or risk of arrhythmic events (such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age)
12. Clinically significant abnormalities of glucose metabolism as defined by any of the following
    a. Diagnosis of diabetes mellitus type I (irrespective of management).or uncontrolled diabetes mellitus type II
    b. Glycosylated haemoglobin (HbA1C) ≥8.0% at screening (64 mmol/mol) (conversion equation for HbA1C [IFCC-HbA1C (mmol/mol) = [DCCT-HbA1C (%) – 2.15] x 10.929)
13. Exposure to potent or moderate inhibitors or inducers of CYP3A4/5 within the following wash-out periods before the first dose of study treatment (for details please refer to Appendix 2).
    a. Inhibitors (competitive): ketoconazole, itraconazole, indinavir, nelfinavir, atazanavir, amprenavir, fosamprenavir, fluconazole, nefazodone, cimetidine, aprepitant, miconazole, fluvoxamine, conivaptan, cyclosporine, imatinib, netupitant, ciprofloxacin, dronedarone, P-glycoprotein, grapefruit juice, or seville oranges (1 week minimum wash-out period), saquinovir, telithromycin, troleandomycin, voriconazole or idelalisib (2 week minimum wash-out period) amiodarone (27 week minimum wash-out period)
    b. Inhibitors (time dependent): erythromycin, clarithromycin, verapamil, ritonavir, diltiazem, bocepravir, cobicistat, danoprevir, elvitegravir, LCL161, lopinavir, mibefradil, posaconazole, telaprevir or tipranivir, ACT-178882, casopitant, crizotinib, darunavir, diltiazem, ledipasvir, lomitapide or tofisopam (2 week minimum wash-out period)

c. Inducers: bosentan, genistein, lersivirine, lopinavir, modafinil, nafcillin, ritonavir, semagacestat, thioridazine, tipranavir (1 week minimum wash-out period), etravirine (2 week minimum wash-out period), phenytoin, rifampicin, St. John's Wort, carbamazepine, dexamethasone, primidone, griseofulvin, carbamazepine, barbiturates, troglitazone, pioglitazone, oxcarbazepine, nevirapine, efavirenz, rifabutin, efavirenz (3 week minimum wash-out period), enzalutimide or phenobarbital (5 week minimum wash-out period), mitotane (114 weeks minimum wash-out period)

14. Exposure to sensitive or narrow therapeutic range substrates of the drug metabolizing enzymes CYP2C8, CYP2C9, CYP2C19, CYP2D6 or the drug transporters Pgp (MDR1), BCRP, OATP1B1, OATP1B3, OCT1 and OCT2 within the appropriate wash-out period before the first dose of study treatment (for details refer to Appendix 2)
15. Application of haemopoietic growth factors (e.g. G-CSF, GM-CSF) within 2 weeks before receiving study drug
16. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that, in the investigator's opinion, gives reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, may affect the interpretation of the results, render the patient at high risk from treatment complications or interferes with obtaining informed consent.
17. History of hypersensitivity to active or inactive excipients of AZD2014 or everolimus or drugs with a similar chemical structure or class to AZD2014 or everlimus
18. History of hypersensitivity to active or inactive excipients of fulvestrant and/or castor oil.
19. Patients presenting with anaemia symptoms (anaemia classed as haemoglobin < 90 g/L).
20. Currently receiving (and are unwilling to discontinue) oestrogen replacement therapy (last dose ≤ 7 days prior to randomisation)
21. Psychological, familial, sociological or geographical conditions that do not permit compliance with the study protocol.
22. Detained persons or prisoners
23. Pregnant or nursing women (including no breast feeding from two weeks before the first dose of study medication, till 8 weeks after the last dose of study medication).

6 PROCEDURES FOR OBTAINING CONSENT AND RANDOMISATION

6.1 Informed Consent

It is the responsibility of the Investigator, or person delegated by the Investigator, to obtain written informed consent from each patient prior to participation in this study, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. Ample time must be given for consideration by the patient before taking part. The PI must also document when the patient information sheet (PIS) was given to the patient in the medical notes as well as the date that the patient gave consent to participate in the trial.

If new safety information becomes available the CI will review the study, update the patient information sheet accordingly and resubmit for relevant regulatory approvals. The CI will review the new safety information and assess whether an urgent IDMC and/or TSC meeting should be convened or whether this information can be reviewed at the next scheduled meeting. All subjects, including those already being treated, should be informed of the new information, given a copy of the revised patient information sheet and give their consent to continue in the study. Patients will not be re-consented following amendments that do not affect safety or number of assessments / visits required.

6.2 Registration and Screening

After ensuring that a patient has given written informed consent, a registration form should be completed by the study site and a copy fax/emailed to the MANTA trial co-ordinator at the Centre for Experimental Cancer Medicine (CECM) using the details below

Centre for Experimental Cancer Medicine

Enquiries: +44 (0) 20 7882 8503
Fax: +44 (0) 20 7882 8409
Email:BCI-MANTA@qmul.ac.uk

The trial coordinator will then assign a unique screening number for the patient and fax back or email as appropriate to the study site. The patients may only then undergo the screening procedures to assess their eligibility, as outlined in section 8.6.

6.3 Randomization

Once it has been confirmed that a patient meets all inclusion and exclusion criteria, they will be randomised to receive fulvestrant, fulvestrant + AZD2014 at a continuous daily schedule, fulvestrant + AZD2014 at an intermittent schedule (2 days on, 5 days off), or fulvestrant + everolimus in a 2:3:3:2 ratio. Randomisation will be stratified by the following two factors:

- measurable disease (measurable vs. non-measurable), and
- sensitivity to prior endocrine therapy (sensitive versus resistant).

  Sensitivity to prior endocrine therapy is defined as (i) at least 24 months of endocrine therapy before recurrence in the adjuvant setting or (ii) a complete or partial response to at least one line of prior metastatic endocrine treatment, or (iii) stabilization for at least 24 weeks of at least one line of endocrine therapy for locally advanced and/ or metastatic breast cancer.

Randomisation will be completed by IWRS. Randomisation will be restarted following the switch from the three-arm to the four-arm version of the study. There is a possibility of a short break in recruitment during this period. Sites will be given access to IWRS. Study staff at sites will then receive the result of the randomisation along with the patient trial number via email generated by IWRS.

Patients should receive their first dose of study treatment no later than 14 days after randomisation.

7 STUDY TREATMENT

7.1 Definition of Investigational Product

Please refer to Pharmacy manual

In the context of this study, AZD2014 and everolimus will be regarded as the investigational products. AstraZeneca will supply the AZD2014 and Fisher Clinical Services will pack, label and distribute AZD2014 to study sites.

The everolimus supply method will vary by country and will depend on local regulations and participating hospital requirements.

In <<insert country – UK, Germany Spain or Portugal>> commercial everolimus will be sourced locally (either by site or Sponsor approved Vendor) and reimbursed by the sponsor of this study. Everolimus will be stored and administerd in keeping with standard local practice and the SmPC.

OR (delete whichever is not applicable)

In <<insert country - France, Hungary, Romania, Georgia or South Korea>> everolimus will be labelled and distributed to sites by Fisher Clinical Services. Everolimus will be stored and administered in keeping with standard local practice and the SmPC.

AZD2014 and everolimus will be dispensed by the study site personnel on an outpatient basis. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Study Treatment and Current Visit forms of the eCRF.

Fulvestrant is used within its licensed indication and will not be regarded as the investigational product. <<delete for South Korea>> Fisher Clinical Services will distribute the supplies to sites. Fulvestrant will be stored, dispensed and administered in keeping with standard local practice and the SmPC.

Study Treatment	Schedule	Dose	Dose increase
AZD2014 (continuous schedule)	Orally, twice daily, continuous daily schedule	50 mg	Not allowed
AZD2014 (intermittent schedule)	Orally, twice daily, days 1 and 2 every week (2 days on; 5 days off)	125 mg [1]	Not allowed
Everolimus	Orally, once daily, continuous schedule	10 mg	Not allowed
Fulvestrant	Two intramuscular (IM) injections, Days 1 & 15 of Cycle 1, and Day 1 of each subsequent 28-day cycle.	500 mg (2 x 250 mg injections)	Not allowed

Table 3: Doses and treatment schedule for AZD2014, everolimus and fulvestrant

7.2 Treatment Schedule

A standard treatment cycle is defined as 4 weeks (Figure 4&5). The start of a cycle will be determined by commencement of fulvestrant. With the exception of the first cycle, during which fulvestrant is administrered on days 1 and 15, fulvestrant will be given on day 1 of each cycle.

In the continous schedule group, AZD2014 will be taken twice daily continuously without a scheduled break (Figure 4). For the intermittent schedule, AZD2014 will be taken twice daily on days 1 and 2 of every week (Figure 5). Everolimus will be taken once daily continuously(without a scheduled break) (Figure 4).

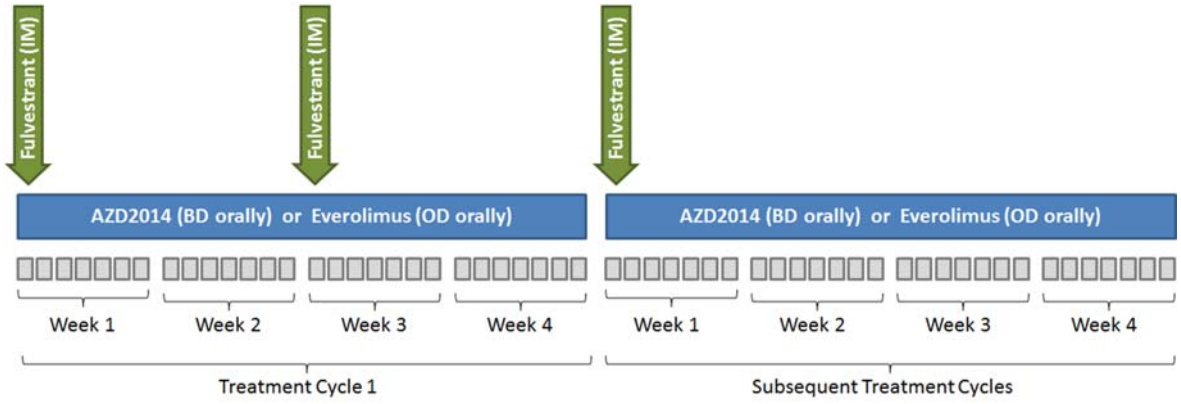

Figure 4: Treatment schedule for fulvestrant + AZD2014 continuous daily and fulvestrant + everolimus arms

[1] If more than 50% of the first 10 patients dosed at 125 mg BID (2 days on, 5 days off) require a dose reduction, the IDMC may decide to reduce the intermittent schedule dose to 100 mg BID (2 days on, 5 days off) or discontinue this treatment arm. Patients dosed at 125 mg BID (2 days on, 5 days off) will not be replaced.

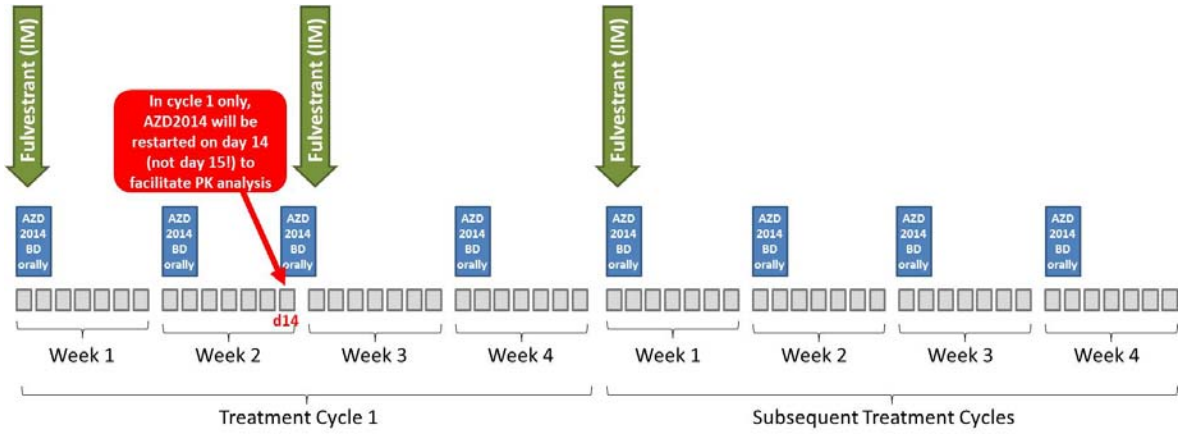

Figure 5: Treatment schedule for fulvestrant + AZD2014 intermittent weekly arm

In cycle 1 only, AZD2014 will be restarted on day 14 (not day 15) to facilitate the PK analysis.

7.2.1 AZD2014

AZD2014 will be provided as 10mg, 25mg and 50mg tablets; the bottles will contain IMP appropriate for dispensing at 4 weekly intervals.

- For the continous daily schedule, AZD2014 will be administered twice daily orally on a continuous schedule at the starting dose of 50mg.
- For the intermittent schedule, AZD2014 will be taken twice daily on days 1 and 2 over every week at a starting dose of 125mg (which may be reduced to 100mg BID based on IDMC review of the first 10 patients dosed at 125mg BID)

Dose modifications are detailed in section 7.6.

Where possible all doses of AZD2014 should be taken at approximately the same times each day, in a fasted state (water to drink only) from at least 2 hours prior to the dose to at least 1 hour post-dose[2]. Twice daily doses should be taken approximately 12 hours apart. If vomiting occurs within 30 minutes after AZD2014 dosing, or later if the tablet(s) can be identified in the vomit content, the patient can re-take new tablet(s).

Should a patient miss a scheduled dose, the patient will be allowed to take the dose up to a maximum of 2 hours after the scheduled dose time. If greater than 2 hours after the scheduled dose time, the following recommendations apply:

- For the continous daily schedule, the missed dose should not be taken and the patient should take the allotted dose at the next scheduled time
- For the intermittent schedule, the missed dose should not be taken on the scheduled day and patients should continue treatment with the next alloted dose. The missed dose should be taken at the next available opportunity 12 hours after the last dose of the week but not later than on day 3 of each week. AZD2014 should not be taken on wash-out days 4-7 of each week.

If a patient needs to take the dose earlier for whatever reason, the patient can take the dose up to 2 hours earlier than the scheduled dose time. The patient should make every reasonable effort to take the AZD2014 tablet(s) on time.

AZD2014 tablets must be swallowed whole and should not be chewed or crushed.

Sunlight protection measures should be adopted during treatment with AZD2014 and should be continued until 3 months after stopping treatment with AZD2014.

[2] Once data have been generated regarding the effect of food on the PK of AZD2014 tablets (to be generated in the Phase I Single Agent Study [D2270C00001]), if it is agreed that the data supports that there is no apparent effect of food on the PK of AZD2014, and if it is so recommended by the TMG, the fasting restriction may be removed.

7.2.2 Everolimus

Everolimus is available as 5mg and 10 mg tablets in packs of 30 tablets per pack (10 tablets in each blister pack) appropriate for dispensing at 4 weekly intervals. For details regarding storage and administration of everolimus, please refer to the everolimus (e.g., AFINITOR) Package Insert or SmPC.

Everolimus will be administered once daily on a continuous schedule at a starting dose of 10 mg. A dose increase of Everolimus is not permitted. Dose modifications are detailed in section 7.6.

Where possible all doses of Everolimus should be taken at approximately the same times each day. If a patient needs to take the dose earlier for whatever reason, the patient can take the dose up to 2 hours earlier than the scheduled dose time. The patient should make every reasonable effort to take the Everolimus tablet(s) on time.

Should a patient miss a scheduled dose, the patient will be allowed to take the dose up to a maximum of 2 hours after the scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose should not be taken and the patient should take the allotted dose at the next scheduled time.

Everolimus should be swallowed whole with a glass of water and the tablets should not be chewed or crushed and grapefruit or citrus juices must be avoided for Everolimus administration. If the tablets cannot be swallowed, the tablets should be disintegrated in approximately 30 ml of water. Immediately prior to administration, the contents should be stirred gently until the tablets have disintegrated into a suspension. The patient should then drink the contents. Afterwards, the glass should be rinsed with an additional 30 ml of liquid and drunk by the patient.

If vomiting occurs no attempt should be made to replace the dose.

7.2.3 Fulvestrant

Fulvestrant will be supplied by AstraZeneca in sterile single-patient prefilled syringes containing 50mg/mL fulvestrant, as a 5-mL injection. For details regarding storage of fulvestrant, please refer to the fulvestrant (e.g., FASLODEX) Package Insert or SmPC.

Fulvestrant 500 mg will be administered in the clinic as two IM injections of 250mg each on Days 1 and 15 of Cycle 1 and Day 1 of each subsequent 28-day cycle. Because AZD2014 may produce subtle changes in clotting efficiency, pressure should be maintained on the injection sites for 3 minutes after injection. For more details regarding the dosing instructions and safety profile of fulvestrant, please refer to the fulvestrant (e.g., FASLODEX) Package Insert or SmPC.

Because fulvestrant is administered intramuscularly, it should be used with caution in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use.

7.3 Duration of treatment

Study treatment will be continued until disease progression unless there is evidence of unacceptable toxicity, or if the patient withdraws from the study.

If *fulvestrant is discontinued* for reasons other than disease progression, the patient may continue on AZD2014 or Everolimus, respectively alone (as applicable) at the investigator's discretion. The patient must continue being scanned for RECIST 1.1 assessment every 12 weeks (±1 week) until objective disease progression (even if further anticancer therapy is administered).

If AZD2014 or Everolimus *is discontinued* for reasons other than disease progression, the patient may continue on fulvestrant alone at the investigator's discretion. The patient must continue being scanned for RECIST 1.1 assessment every 12 weeks (±1 week) until objective disease progression (even if further anticancer therapy is administered).

If a patient becomes amenable to surgery or ablative therapy, she has to be withdrawn from study and will be censored-assessed for PFS at the date of surgery/ablative therapy.

7.4 Premedication

Routine premedication is not required for fulvestrant, AZD2014 or everolimus.

7.5 Concomitant treatment

All concomitant medication from the time the patient provides written informed consent until the end of treatment visit must be recorded on the electronic Case Report Form (eCRF). Additionally, any diagnostic, therapeutic or

surgical procedure performed during the study period, should be recorded including the date, indication, description of the procedures(s) and any clinical findings. If medically feasible, patients taking regular medication, with the exception of potent or moderate inhibitors or inducers of CYP3A4/5 or CYP2C8, should be maintained on it throughout the study period.

7.5.1 Recommended concurrent therapy

The following therapies are recommended during study participation, as applicable:

- No prophylactic anti-emetic therapy is planned for AZD2014 or everolimus but standard anti-emetic therapy including a 5-HT3-antagonist can be given as needed on a prophylactic and treatment basis in compliance with the standards of the centre.
- Loperamide for symptomatic treatment of diarrhoea ≥ grade 2 (details provided in section 7.6.2.6).
- Blood transfusions are allowed at any time during the study. Patients already receiving erythropoietin at the time of screening for the study may continue it providing they have been receiving it for more than one month at the time study treatment is started.
- Patients may receive bisphosphonate or denosumab therapy for the treatment of bone metastases, but initiation of bisphosphonate or denosumab therapy or modification of the pre-study bisphosphonate or denosumab treatment regimen for bone metastasis requires the approval of the Medical Monitor.
- Patients may take corticosteroids, however, increased vigilance is recommended on electrolyte and/or glucose levels due to the potential for corticosteroid-related metabolic disturbance.
- Cases of pneumocystis jirovecii (carinii) pneumonia (PJP, PCP), some with fatal outcome, have been reported in patients who received everolimus. PJP/PCP may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis for PJP/PCP should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required for patients receiving everolimus.

- Supportive care and other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the CRF.

7.5.2 Prohibited concurrent therapy

- Other anticancer agents, investigational agents and radiotherapy should not be given while the patient is on study treatment, although radiation for palliation at focal sites is permitted (as long as the radiation field covers less than 30% of the marrow and does not include whole pelvis or spine; disease progression in the bones has to be excluded by appropriate imaging investigations).
- Application of haemopoietic growth factors (e.g. G-CSF, GM-CSF) within 2 weeks before receiving study drug
- Concomitant use of moderate or potent CYP3A4/5 and/or CYP2C8 inhibitors (for details please refer to Appendix 2) as these agents may increase the plasma levels of AZD2014 or Everolimus.
- Concomitant use of moderate or potent CYP3A4/5 and/or CYP2C8 inducers (for details please refer to Appendix 2) as these agents may decrease the plasma levels of AZD2014 or Everolimus.
- Concomitant use of known or potential substrates of the drug metabolizing enzymes CYP2C8, CYP2C9, CYP2C19, CYP2D6, or the drug transporters Pgp (MDR1), BCRP, OATP1B1, OATP1B3, OCT1 and OCT2 (for details please refer to Appendix 2) as co-treatment may lead to their higher exposure, particularly at the higher dose AZD2014 schedule
- Chronic systemic corticosteroid use (≥10 mg of prednisone or an equivalent dose of other anti-inflammatory corticosteroids) for ≥28 days or use of other immunosuppressants
- The use of live attenuated vaccines should be avoided during treatment with Everolimus or AZD2014. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG (Bacillus Calmette-Guérin), yellow fever, varicella, and TY21a typhoid vaccines

7.6 Dose Modification and Delay

Toxicities are graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Dose reductions are to be made according to the system showing the greatest degree of toxicity. Patients' safety will be monitored on an ongoing basis during this study.

If a patient experiences a clinically significant and/or unacceptable toxicity felt to be possibly related to AZD2014, everolimus and/or fulvestrant, dosing may be interrupted at the investigators discretion, and supportative therapy administered as required. Listed below are only recommendations to assist with toxicity management of AZD2014 and everolimus, whereas local guidelines and standard clinical practice should be followed regarding fulvestrant dose adjustments for toxicities.

If toxicity is seen with AZD2014 or everolimus requiring discontinuation or delay in dosing, Fulvestrant dosing may continue. If toxicity is seen with Fulvestrant requiring discontinuation or delay in dosing, AZD2014/everolimus dosing may continue.

Study Treatment	Starting Dose	Dose reduction levels	Dose increase levels
AZD2014 (continuous schedule)	50mg BD	Reduction level 1: 35mg BD Reduction level 2: 25mg BD	Dose increase not permitted
AZD2014 (intermittent schedule; 2 days on; 5 days off)	125mg BD	Reduction level 1: 100mg BD	Dose increase not permitted
Everolimus	10mg OD	Reduction level 1: 5mg OD Reduction level 2: 5mg every other day	Dose increase not permitted
Fulvestrant	500mg	Dose reductions not permitted.	Dose increase not permitted

Table 4: Dose modification levels for AZD2014, everolimus and fulvestrant

7.6.1 Fulvestrant

Fulvestrant dose adjustments for toxicities are not permitted.

If receipt of fulvestrant is suspended for 28 continuous days from the scheduled day of administration (i.e. interrupted for more than one cycle), this study therapy should be permanently withdrawn. Any request to continue therapy after such a suspension must be agreed with the Chief Investigator.

7.6.2 Dose reductions and delays for AZD2014 and Everolimus

If a patient experiences toxicities that are *CTCAE ≥Grade 3 or clinically significant* and/or experiences *unacceptable toxicity* not attributable to the disease or disease-related processes under investigation, AZD2014/everolimus dosing will be withheld for up to 28 days until toxicity improves to CTCAE Grade ≤2 or becomes clinically tolerable. Supportive therapy should be administered as required.

- If toxicity *improves to ≤ CTCAE Grade 2* within 28 days of AZD2014/everolimus dose interruption reinstate AZD2014/everolimus at a *reduced dose* (1 dose level) maintaining treatment for toxicity as necessary.
- Where a CTCAE Grade ≥3 or clinically significant or intolerable toxicity *does not improve* to a lower CTCAE Grade within 28 days of AZD2014/everolimus dose interruption, AZD2014/everolimus should be *permanently discontinued*.

Re-escalation is not permitted.

If receipt of AZD2014 or Everolimus is suspended for more than 28 continuous days for any reason this study therapy should be permanently withdrawn.

Specific dose management for myelosuppression, elevation of liver enzymes, hyperglycaemia, metabolic events, skin reactions, stomatitis, diarrhoea, pneumonitis, ECG-changes and haematological toxicities are detailed below:

7.6.2.1 Myelosuppression

AZD2014/everolimus should be withheld where neutrophils <0.5 x10^9/L and platelets <25 x10^9/L, or non-traumatic bleeding with platelets: 25 to <50 x10^9/L.

7.6.2.2 Elevation of Liver function tests (LFTs)

If a patient exhibits an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) result in excess of 10 x ULN, or AST or ALT in excess of 8 x ULN in combination with a doubling of bilirubin from baseline, which is considered to be related to study drug, they will not be permitted to restart AZD2014/everolimus.

7.6.2.3 Hyperglycaemia

Recommendations for the management of hyperglycaemia are summarized in Table 5. Patients with hyperglycaemia should be instructed to follow the dietary guidelines provided by the American Diabetes Association.

Metformin is currently recommended for the management of hyperglycaemia occurring in patients participating in studies of PI3K and mTOR inhibitors. Investigators should exercise caution in the dosing and management of patients receiving the metformin/AZD2014 or metformin/Everolimus combination and must be vigilant for signs of renal impairment and metformin toxicity, such as lactic acidosis and hypoglycaemia, namely: lethargy, hypotension, poor urine output, drowsiness, irritation, tachypnoea, sweating, diarrhoea, and vomiting.

Metformin should only be given on the days when AZD2014/everolimus is also administered and should be withdrawn when treatment with AZD2014/everolimus is withdrawn, unless otherwise clinically indicated. Due to the potential interaction of metformin and AZD2014/everolimus due to inhibition of OCT2 when taking both AZD2014/everolimus and metformin concurrently, patients should attend the clinic for monitoring of serum creatinine at least once per week for the first 3 weeks after initiation of metformin, then every 3 weeks thereafter. Metformin should be given as per local standard procedures.

In the case of patients developing severe hyperglycemia, patients may require treatment in an intensive care unit. Due to the predicted short half life of AZD2014, only a short period of insulin resistance is expected. Therefore early treatment with high doses of insulin should be carefully evaluated and blood sugars monitored as per standard clinical practice.

Grade	Description	Symptoms	Modification of AZD2014/ everolimus treatment
Grade 1	Fasting glucose >ULN -160 mg/dL (>ULN - 8.9 mmol/L)	NA	No intervention required
Grade 2	Fasting glucose >160 -250 mg/dL (>8.9 - 13.9 mmol/L)	NA	Check at next visit; if persistent, consider starting or adjusting oral anti-hyperglycemic agent
Grade 3	Fasting glucose >250 - 500 mg/dL (>13.9 - 27.8 mmol/L)	Asymptomatic, OR Symptomatic [1] OR Severe symptoms [2] or requiring hospitalisation	Hold until Grade ≤1; Consider starting or adjusting oral anti-hyperglycemic agent. Restart at the next lower dose level.
Grade 4	Fasting glucose value >500 mg/dL (>27.8 mmol/L)	Non-life threatening OR Life threatening	Discontinue AZD2014/everolimus

Table 5: Summary of recommendations for the management of hyperglycaemia

7.6.2.4 Metabolic Events

Recommendations for the management of metabolic events (e.g. dyslipidaemia) are summarized in Table 6.

Grade	Modification of AZD2014/ everolimus treatment
Grade 1	No dose adjustment required.
Grade 2	No dose adjustment required.
Grade 3	Hold until Grade ≤1; Restart at the next lower dose level.
Grade 4	Discontinue AZD2014/everolimus

Table 6: Summary of recommendations for the management of metabolic events

7.6.2.5 Stomatitis/Oral mucositis

Recommendations for the management of stomatitis/oral mucositis are summarized in 7. Early identification and intervention is critical for the optimal management of mucositis.

Patients who develop oral mucositis which requires intervention and/or dose modification or interruption should be asked to rinse their mouth with several mouthfuls of water between 1 and 2 hours after administration of AZD2014/everolimus. The water may be swallowed or spat out according to the patient's preference.

[1] Symptoms of hyperglycaemia include blurry vision, polydipsia, and polyuria

[2] Severe symptoms of hyperglycaemia include neurological symptoms (lethargy, focal signs, or obtundation), hyperventilation, abdominal pain and hypotension

For more severe toxicity (Grade 2 or 3), the suggested treatments are topical analgesic mouth treatments (ie, local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol), with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (eg, Kenalog in Orabase®).

Agents containing hydrogen peroxide, iodine, and thyme derivatives may worsen mouth ulcers. It is preferable to avoid these agents.

Grade	Description	Symptomatic treatment	Modification of AZD2014/ everolimus treatment	Recommendations for future events
Grade 1	Asymptomatic or mild symptoms; intervention not indicated	use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times daily until resolution.	Treatment can be continued without a dose reduction.	No specific recommendations
Grade 2	Moderate pain; not interfering with oral intake; modified diet indicated	Topical analgesic mouth treatments (ie, local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol), with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (eg, Kenalog in Orabase®);	May continue with a dose reduction at the investigators discretion; If resolves to ≤ Grade 1 within 14 days of onset, treatment may be restarted, at the same dose or a lower dose. If stomatitis does not resolve to ≤ Grade 1 after 14 days, then the patient should be withdrawn from the study	If Grade 2-3 stomatitis recurs, reduce AZD2014/ everolimus after discussion with the Medical Monitor.
Grade 3	Severe pain; interfering with oral intake	Topical analgesic mouth treatments (ie, local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol), with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (eg, Kenalog in Orabase®);	Should be stopped until stomatitis improves to ≤ Grade 1. If resolves to ≤ Grade 1 within 14 days of onset, treatment may be restarted, at the next lower dose. If stomatitis does not resolve to ≤ Grade 1 after 14 days, then the patient should be withdrawn from the study	If Grade 2-3 stomatitis recurs, reduce AZD2014/ everolimus after discussion with the Medical Monitor.
Grade 4	Life-threatening consequences; urgent intervention indicated	Topical analgesic mouth treatments (ie, local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol), with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (eg, Kenalog in Orabase®);	Permanently discontinue AZD2014/everolimus	Not applicable

Table 7: Summary of recommendations for the management of stomatitis/oral mucositis

7.6.2.6 Diarrhoea

Early identification and intervention is critical for the optimal management of diarrhoea. A patient's baseline bowel patterns should be established so that changes in patterns can be identified while patient is on treatment.

It is recommended to give patients a prescription of loperamide with instructions to start loperamide at the onset of diarrhoea as per the recommendations outlined below. Patients should be instructed to first notify their physician/healthcare provider at onset of diarrhoea of any severity.

Loperamide: Loperamide should be administered at an initial dose of 4mg followed by 2mg after every unformed stool. If diarrhoea is resolving loperamide should be continued at a 2mg dose after every unformed stool until diarrhoea free (<Grade 1/bowel patterns back to baseline) for 12 hours. If diarrhoea recurs, re-initiate loperamide treatment as needed to maintain normal bowel patterns.

If diarrhoea is not resolving administer loperamide at 2mg every 4 hours for the next 24 hour. Re-evaluate after 24 hours; if diarrhoea is resolving, administer loperamide at 2mg after every unformed stool until diarrhoea free (<Grade 1/bowel patterns back to baseline) for 12 hours. If diarrhoea is not resolving continue loperamide at 2mg q4 hours and re-evaluate every 24 hours.

If diarrhoea persists for more than 1 week with loperamide, consider treatment with second-line agents (i.e., octreotide, budesonide or tincture of opium).

Dietary modifications which are essential in the management of diarrhoea include the following recommendations:

- Stop all lactose containing products and eat small meals
- Avoid spicy, fried/fatty foods, raw vegetables or other foods high in fibre
- Eat foods low in fibre (i.e., lean meat, rice, skinless chicken, fish, eggs, cooked skinless fruits, cooked/pureed vegetables)
- Avoid caffeine/alcohol as they can irritate the bowel & increase motility
- Hydration: Drink 8-10 large glasses of clear liquids a day (e.g., water, electrolyte drink).
- Avoid acidic drinks such as tomato juice and fizzy soft drinks
- Supplement diet to include foods rich in potassium (bananas, potatoes, apricots)

Severe or significant diarrhoea: The following guidelines should be followed in case of diarrhoea of CTCAE Grade ≥3 or diarrhoea that is clinically significant or intolerable and causally related to treatment with AZD2014/everolimus

- Initiate appropriate anti-diarrhoeal treatment.
- If clinically appropriate or if toxicity does not improve to CTCAE Grade <2 or remains clinically intolerable, despite optimal treatment, *withhold AZD2014/everolimus for up to 28 days*.
- *If toxicity improves* to CTCAE Grade <2 or becomes clinically tolerable reinstate AZD2014/*everolimus*, as clinically appropriate, at either the *current dose or at a reduced dose* (1 dose level) maintaining treatment for toxicity as necessary.
- Where a CTCAE Grade ≥3 or clinically significant or intolerable toxicity *does not improve* after 28 days of AZD2014/*everolimus* dose interruption, AZD2014/*everolimus* should be *permanently discontinued*.

Recurrence of severe or significant diarrhoea: on recurrence of a CTCAE Grade ≥3 or clinically significant or intolerable toxicity, reinstate treatment as required.

- If toxicity does not improve to CTCAE Grade <2 or remains clinically significant or intolerable, despite optimal treatment, withhold dose for up to 28 days until improvement of toxicity.
- If toxicity improves to CTCAE Grade <2 or becomes clinically tolerable reinstate AZD2014/*everolimus*, as clinically appropriate, at either the current dose or at a reduced dose (up to two dose level reductions) maintaining treatment for toxicity as necessary.

7.6.2.7 Rash/Skin toxicity

Early identification and intervention is critical for the optimal management of skin toxcity and rash. The currently available clinical evidence suggests that antihistaminergic drugs may ameliorate the occurance and severity of rash associated with treatment with AZD2014. Therefore, patients who are experiencing any changes in the condition of their skin whilst on treatment with AZD2014 or everolimus should be considered for treatment with oral antihistamines, in order to prevent the development of clinically relevant skin toxicity/rash.

Patients who develop skin rash, characterised by dry skin, pruritis, or acneform rash may require an interruption in treatment. Treatment with topical steroid cream/ointment and/or antihistamines and antibiotics should be considered early.

Recommendations for the management of rash and other skin toxicity are summarised in Table 8. Examples for topical or systemic treatment for skin toxicity are provided below:

- **Topical steroids:** Triamcinolone acetonide 0.025%: Desonide 0.05%; Fluticasone proprionate 0.05%, Aclometasone 0.05%
- **Topical antipruritics:** Pramoxine 1%; Doxepin 5% cream
- **Oral antihistamines:** Loratidine, cetirizine, Fexofenadine; Diphenhydramine 25-50 mg every 8h; Hydroxyzine 25 mg every 8h;
- **Topical antibiotics:** Clindamycin 1-2%; Erythromycin 1-2%; Metronidazole 1%; Silver sulphadiazine1%
- **Oral antibiotics:** Doxycycline 100 mg bid; Minocycline 100 mg bid; Oxytetracycline 500 mg bid

Adverse event	Grade	Description	Symptomatic treatment	Modification of AZD2014/ everolimus treatment	Recommendations for future events
Dry skin/ Xerosis	Grade 1	Covering <10% BSA and not associated erythema or pruritus	**Face/Body:** Over the counter moisturizing cream or ointment plus consider oral antihistamines. **Body:** Ammonium lactate 12% cream BID or 6% salicylic acid cream BID plus consider oral antihistamines	Treatment can be continued without a dose reduction.	No specific recommendations
	Grade 2	Covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental ADL			
	Grade 3	Covering >30% BSA and associated with pruritus; limiting self care ADL	**Same as for Grade 1.** Consider treatment with topical steroid cream/ointment and/or antihistamines. Add topical steroids for eczematous areas	Interrupt AZD2014/ everolimus until AE improves to ≤ Grade 1 or baseline.	If AE improves to ≤ Grade 1 or baseline within 2 weeks – reduce AZD2014/ everolimus one dose level. If AE lasts >2 weeks, discontinue AZD2014/ everolimus.
Pruritus	All grades		Same as for dry skin/xerosis, only **add topical steroids** (moderate strenght) or topical antipuritic BID		
Rash	Grade 1	Macules, papules and/or pustules covering <10% BSA, with or without symptoms (pruritus, burning, tenderness)	**Face/Body:** Over the counter moisturizing cream or ointment plus consider oral antihistamines. **Body:** Ammonium lactate 12% cream BID or 6% salicylic acid cream BID Consider treatment with oral antihistamines – if no improvement, add topical steroid cream/ointment and/or **topical antibiotic BID or oral antibiotics for 6 weeks.**	Treatment can be continued without a dose reduction.	No specific recommendations
	Grade 2	Macules, papules and/ or pustules covering 10-30% BSA, with or without symptoms (pruritus, burning, tenderness, skin changes, oedema, papulation, excoriation etc); associated with psychosocial impact; limiting instrumental ADL	Same as for grade 1; If topical antibiotic has been used, switch to oral antibiotic for 6 weeks		
	Grade 3	Macules, papules and/or pustules covering >30% BSA, with or without symptoms (pruritus, burning, tenderness, skin changes, oedema, papulation, excoriation etc); associated with psychosocial impact; limiting self care ADL;	Same as for grade 1; **Add oral antibiotics for 6 weeks**; switch to broad spectrum/gram negative cover if infection suspected (yellow crusts, purulent discharge, painful skin/nares); consider swap for bacterial culture	Interrupt AZD2014/ everolimus until rash improves to ≤ Grade 1 or baseline.	If rash improves to ≤ Grade 1 or baseline within 2 weeks – reduce AZD2014/ everolimus one dose level. If rash lasts >2 weeks, discontinue AZD2014/ everolimus.

Table 8: Summary of recommendations for the management of rash/skin toxicity

7.6.2.8 Pneumonitis

All patients with suspected pneumonitis or persistant cough or dyspnoea for >14 days, without clinical symptoms of airway infections, should have further investigations to diagnose or rule out pneumonitis. This includes a CT scan of the chest (ideally a high-resolution CT scan) and may include a complete pulmonary function test including 3 forced expiratory volumes, forced vital capacity and carbon monoxide diffusing capacity (DLco% & DLco) if clinically indicated. A recent haemoglobin measurement should also be available at the time of the DLco evaluation if applicable.

For any new respiratory symptoms (eg, cough, dyspnoea, lower respiratory infection) not clearly explained by other factors (eg, dyspnea associated with substantial drop in haemoglobin), patients should have oxygen saturation measured. If <92%, the (high resolution) CT scan of the chest should be repeated and pulmonary function tests should be performed.

In case of grade 2 pneumonitis consider interruption of AZD2014/everolimus dose until improvement to Grade ≤1. Restart treatment at the next lower dose level. Repeat CT scan every 4 weeks until return to baseline. Consider bronchoscopy. Prescribe corticosteroids if cough is troublesome. Interrupt treatment as long as corticosteroids are being given. Discontinue treatment if recovery to Grade ≤1 is not evident within 28 days.

In case of grade 3 pneumonitis interrupt treatment until improvement to Grade ≤1. Repeat CT scan every 4 weeks until return to baseline. Bronchoscopy recommended. Prescribe corticosteroids if infectious etiology is ruled out. Taper as clinically indicated. Restart therapy within 28 days at a reduced dose if clinical benefit is evident. Interrupt treatment as long as corticosteroids are being given. If toxicity recurs at grade 3, consider discontinuation of AZD2014/ everolimus.

In case of grade 4 pneumonitis discontinue treatment. Repeat CT scan every 4 weeks until return to baseline. Bronchoscopy recommended. Prescribe corticosteroids if infectious etiology is ruled out. Taper as clinically indicated.

7.6.2.9 ECG Changes

Patients who develop persistent, confirmed T wave repolarisation abnormalities (inversion or flattening) on regularly scheduled ECGs should have a troponin measurement within 24 hours of first recording the ECG changes (and as clinically indicated) and a follow up ejection fraction measurement determined within 2 weeks using the same technology used at baseline (ECHO or MUGA). ECG assessments should be repeated every 2 weeks until recovery off treatment (or as clinically indicated).

Patients with T wave repolarisation abnormalities without any other clinical relevant cardiac findings can continue study treatment.

Study treatment with AZD2014/everolimus has to be discontinued in case of clinical relevant cardiac findings (e.g. myocardial infarction) or significant QTc prolongation (>500 msec or >60 msec longer than the pre-dose baseline value).

7.6.2.10 Haematological Toxicities

Recommendations for the management of haematological toxicities are summarised in Table 9.

Event	Grade	Description	Modification of AZD2014/ everolimus treatment
Platelet count decreased	Grade 1	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	No intervention required
	Grade 2	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	Hold until recovery to Grade ≤ 1; restart at same dose level as before.
	Grade 3	<50,000 - 25,000/mm^3; <50.0 - 25.0 x 10^9 /L	Hold until recovery to Grade ≤ 1; restart at next lower dose level.
	Grade 4	<25,000/mm^3; <25.0 x 10e9 /L	Hold until recovery to Grade ≤ 1; restart at next lower dose level.
Neutrophil count decreased	Grade 1	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	No intervention required
	Grade 2	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	No intervention required
	Grade 3	<1000 - 500/mm^3; <1.0 - 0.5 x 10^9 /L	Hold until recovery to Grade ≤ 2; restart at same dose level as before.
	Grade 4	<500/mm^3; <0.5 x 10^9 /L	Hold until recovery to Grade ≤ 2; restart at next lower dose level.
Febrile neutropenia	Grade 3	ANC 38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour	Hold until recovery to Grade ≤ 2; restart at next lower dose level.
	Grade 4	Life-threatening consequences; urgent intervention indicated	Discontinue treatment

Table 9: Summary of recommendations for the management of haematological toxicities

7.7 Drug Supplies and Labelling

7.7.1 Provision

AstraZeneca will supply AZD2014 and Fulvestrant. Fisher Clinical Services will pack, label and supply AZD2014 and Fulvestrant to study sites.

The everolimus supply method will vary by country and will depend on local regulations and participating hospital requirements.

In <<insert country – UK, Germany, Spain or Portugal>> commercial everolimus will be sourced locally (either by site or Sponsor approved Vendor) and reimbursed by the sponsor of this study.

OR (delete whichever is not applicable)

In <<insert country - France, Hungary, Romania, Georgia or South Korea>> everolimus will be labelled and distributed to sites by Fisher Clinical Services.

Patients will be supplied with sufficient medication for each visit. There will be sufficient tablets of AZD2014 and/or everolimus to cover the visit window plus overage. Fulvestrant will be stored, dispensed and administered in keeping with standard local practice.

Patients enrolled in the study will be dispensed bottles of AZD2014, packs of Everolimus or Fulvestrant by local hospital pharmacies as determined by IWRS and randomisation scheme.

7.7.2 Labelling and Storage

In <<insert country – UK, Germany Spain or Portugal>> AZD2014 and fulvestrant will be labelled and distributed by Fisher Clinical Services. Everolimus will be labelled in accordance with local regulations. All drug labels will contain information to meet the applicable regulatory requirements.

OR (delete whichever is not applicable)

In <<insert country - France, Hungary, Romania, Georgia or South Korea>> AZD2014, Fulvestrant and everolimus will be labelled and distributed by Fisher Clinical Services.

Study drug labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

The label will include the following information:

- Name, address and telephone number of sponsor
- IP/study drug dosage form, route of administration, and quantity of dosage units.
- Storage conditions.
- Study code.
- Enrolment code
- Directions for use

All study drugs should be kept in a secure place under appropriate storage conditions. The IP label on the bottle specifies the appropriate storage.

7.7.3 Ordering of Study medication

Upon site activation in the IWRS by the CTU or Sponsor the IWRS will raise an order automatically for initial drug to be sent to the site. Subsequent orders are automatically done by the IWRS based on trigger levels, sites will not have to request material

In <<insert country – UK, Germany Spain or Portugal>> individual sites (or Sponsor approved Vendor) will be responsible for ensuring adequate supplies of everolimus. <<delete for France, Hungary, Romania, Georgia or South Korea>>

7.7.4 Pharmacy Responsibilities

At the time of the dispensing, the pharmacist should complete the required details on each label. AZD2014 and everolimus will normally be dispensed immediately following randomisation. The start and stop dates of treatment will be recorded in the CRFs.

Each pharmacy department must designate a responsible person for ensuring that:

- Investigational products are handled and stored safely and properly
- Investigational products are dispensed only to trial patients and in accordance with the protocol
- Any unused products are destroyed according to local practice

It is the responsibility of the pharmacist to ensure adequate stock of all study medications is available.

7.7.5 Application and Accountability

AZD2014 and everolimus are planned as a self-administered outpatient treatment. The patient should be encouraged to take the required doses according to the treatment plan. Any omissions should be reported to the investigator or the study nurse and recorded by the patient in their study diary and in the CRF by the site staff together with the reason for the omission. Any dispensed but unused drug at the end of each treatment period should be counted and noted on the CRF to calculate the total dose received by the patient.

All unused or returned medication, after drug accountability, should be destroyed locally.

Full drug accountability records must be maintained for **AZD2014, fulvestrant and everolimus** using the IMP accountability logs provided. Sites may amend the IMP accountability logs provided or use their own documentation if it captures all the information required by the Sponsor.

7.8 Termination of treatment and/or study participation

Patients will be informed that they have the right to withdraw from the treatment or the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Confirmed objective disease progression assessed by RECIST 1.1.
- Patients incorrectly initated on IMP
- Patient becomes pregnant
- Intercurrent illness that, in the judgment of the investigator, will affect assessments of clinical status to a significant degree
- Unacceptable toxicity
- Determination by the investigator that it is no longer safe for the patient or in the patient's best interest to continue therapy
- Patient request
- Protocol violations or severe non-compliance with study protocol in the judgement of the investigator and/or the sponsor
- Clinical need for concomitant or ancillary therapy (i.e., non–protocol-specified anti-cancer therapy) that is not permitted in the study
- Administrative reasons
- General or specific changes in the patient's condition that are unacceptable for further treatment in the judgment of the investigator

The primary reason for a patient's withdrawal from the study is to be recorded on the CRF. At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed.

7.9 Study Discontinuation

The sponsor and the TMG have the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrolment is unsatisfactory.
- Data recording is inaccurate or incomplete

8 STUDY ASSESSMENTS

8.1 Definition of Study Assessments

8.1.1 Safety Evaluations

8.1.1.1 Clinical safety

The following tests will be performed prior to and/or on specified days during and following therapy:

- Complete medical history including diagnosis of cancer, histology, menopausal status, and comorbidities
- Concomitant medications (includes prescription medications and over-the-counter preparations) used by the patient from the time the patient provides written informed consent and during the study until the end of treatment visit will be documented.
- Toxicity/symptoms evaluation
- Physical examination
- Vital signs including weight, height, heart rate and blood pressure
- ECOG Performance Status

- Diffusion coefficient (DLCO) to evaluate lung function (at screening and only if clinically indicated thereafter)

8.1.1.2 Laboratory Determinations

The following tests will be performed by a local laboratory:

- Haematology including full blood count with WBC, ANC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count and haemoglobin
- Serum chemistry including Mg (at screening only), Ca, Na, K, glucose, AST, ALT, alkaline phosphatase, bilirubin, creatinine, protein
- HbA1c and lipid panel including total cholesterol, high-density lipoprotein, low-density lipoprotein and triglycerides (at screening, weeks 8, 16, 24and every 12 weeks thereafter)
- INR, aPTT (screening only)

All patients with clinically significant abnormal laboratory results are to be followed until the results return to normal ranges or until a valid reason, other than a drug-related adverse event, is identified.

8.1.1.3 ECG Measurements

Serum potassium and calcium levels must be within normal limits before recording ECGs, as determined by local laboratory testing. Patients with hypokalemia may receive IV or oral potassium per institutional standard practice to bring potassium levels within normal limits prior to recording ECGs. Retesting of serum potassium levels should be performed according to institutional standard practice.

Baseline 12-lead ECG readings (triplicate measurements) will be taken during the screening period and at certain visits throughout the trial (refer to section 8.6 and 8.7). To minimize variability in autonomic tone and heart rate, it is important that patients are resting quietly and in a supine position for at least 5 minutes prior to recording ECGs. Blood draws and other procedures should be avoided during the period immediately before ECG measurement, and activity should be controlled as much as possible to minimize variability due to the effects of physiologic stress. If possible, the same machine should be used for all ECGs for a specific patient. Triplicate runs of 12-lead ECG measurements must be obtained at each assessment time point and should be collected as three recordings in close succession over a period of not more than 2 minutes.

Guidance on dose management for ECG-changes are detailed in section 7.6.2.9.

If at a particular post-dose time point, the mean QTc is >500msec or >60msec longer than the pre-dose baseline value, another ECG must be recorded within the next 5 minutes. If the QT/QTc prolongation is confirmed on repeat ECG triplicate, single ECG recordings should be repeated at least hourly until two successive ECGs show QTc values below the threshold value that triggered the repeated measurement. The investigational site should immediately notify the Medical Monitor of any QTc-confirmed values that are > 500 msec and reflect a change > 60msec from baseline.

In addition to the ECG, left ventricular ejection fraction (LVEF) is to be determined during screening using the ECHO or MUGA technology. Bidimensional echocardiography (ECHO) is the preferred modality because of the global technetium [Tc-99m] shortage (but MUGA can be used alternatively). The same method used at screening should be used throughout the study.

8.1.2 Tumour assessments

RECIST 1.1 criteria will be used to assess patient response to treatment by determining PFS, overall response rate (ORR), change in tumour size at 16 weeks, clinical beneft rate (CBR), duration of response and duration of clinical benefit. The RECIST 1.1 guidelines for measurable, non-measurable, target, and non-target lesions (NTL) and the objective tumour response criteria (CR, PR, stable disease [SD], or progressive disease [PD]) are presented in Appendix 3.

Tumour assessments: Screening assessments will be performed using contrast-enhanced CT scans of the chest, abdomen and pelvis, with additional anatomy as clinically indicated by extent of disease[3]. Subsequent tumour assessments should include CT scans of the chest and abdomen and other sites of disease. MRI scans may be substituted for CT scans but MRI of the chest may only be performed with approval from the Sponsor. Additional anatomy may be imaged at follow-up on suspicion of new lesions.

Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of

[3] Patients who cannot tolerate CT with contrast, despite pre-medications, may undergo a non-contrast CT scan of the chest and MRI of the abdomen.

individual patients. Baseline assessments should be performed no more than 28 days before the start of study treatment, and ideally should be performed as close as possible to the start of study treatment. The same radiographic procedure used to define measurable disease sites at screening must be used throughout the study (e.g., the same contrast protocol for CT scans).

Tumour assessments will be performed at screening (within 28 days prior to Day 1 of Cycle 1), every 8 weeks (±7 days) during the first 40 weeks, every 12 weeks (±7 days) thereafter, and when clinically indicated for all patients, including those with bone-only disease. This schedule is to be maintained and will not be shifted for treatment delays. If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression then the patient should still continue to be followed until objective disease progression as defined by RECIST 1.1, death or withdrawal of consent, whichever occurs first.

Bone scans: An initial bone scan should be performed within 6 weeks prior to Day 1. For patients without known or suspected bone metastasis, follow-up bone scans are not required. Bone scans should only be repeated in the event of clinical suspicion of progression of existing bone lesions that cannot be visualised on CT or MRI, the development of new bone lesions or in the assessment of a CR, if any disease was evident at screening. For patients with **bone-only disease** not visible on the CT or MRI scans being performed as part of tumour assessments, a bone scan should be repeated every 12 weeks (+/-7 days) and when clinically indicated.

Additional scans*:* Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

Evaluation: Equivocal new lesions may be further evaluated by other modalities (biopsy, positron emission tomography, MRI, or CT scans, or plain radiographs). If the lesions remain equivocal, the investigator should use his or her judgment with regard to recording the finding as a new lesion on the Tumour Evaluation CRF. If a new lesion is recorded, the tumour response should be recorded as progressive disease. If the lesion remains equivocal and in the investigator's opinion is likely not reflective of progressive disease, the lesion should not be recorded as a new lesion, and the patient may remain on study drug. This applies to new lesions identified by bone scan or any tumour assessment modality.

Categorisation of objective tumour response assessment will be based on the RECIST 1.1 criteria of response: CR, PR (partial response), SD (stable disease) and PD (progression of disease). Target lesion (TL) progression will be calculated in comparison to when the tumour burden was at a minimum (i.e. smallest sum of diameters previously recorded on study). In the absence of objective progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

If the Investigator is in doubt as to whether objective progression has occurred, particularly with response to NTL or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment and reassess the patient's status. Alternatively, repeat assessments might be scheduled earlier if clinically indicated. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of objective progression.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in 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 NTLs is usually not sufficient to quality for unequivocal progression status.

The primary PFS analysis for this study will be based on local review at participating centres. In addition, all radiographs including bone scans obtained as part of the protocol-required tumour assessments (including interval assessments obtained that documented progression of disease if applicable or for confirmation of objective response, if performed) will also be submitted to an IRF which will be the basis for a secondary PFS analysis and also for secondary analysis of all other efficacy endpoints.

Radiological examinations performed in the conduct of this study for RECIST response assessments must be retained at site as source data and a copy anonymised for personal identifiers, e.g. name, initials, be available for collection by the Sponsor to support any future regulatory requests.

8.1.3 Patient-Reported Outcomes

Overall QoL will be measured using the Functional Assessment of Cancer Therapy – General (FACT-G) questionnaire together with 2 standardised and validated subscales the FACT-Anti-A, and FACT-ES. Participation of patients in these QoL assessments will depend on the availability of the questionnaires in the local language. **In <insert country> patients will be given the <insert available questionnaires> questionnaires to complete.**

All these have been used to determine cancer and breast-cancer specific quality-of-life and symptoms in numerous surgical and novel systemic therapy clinical trials assessing the efficacy and safety. .

The questionnaires will be administered at baseline prior to randomisation and returned to the co-ordinating QoL centre. Thereafter patients should complete questionnaires prior to certain scheduled visits (refer to section 8.6 and

8.7) with the physician during the study treatment period, and at the End of Treatment Visit.

The Functional Assessment of Cancer Therapy – General (FACT-G) scale is a 27 item, self administered, multi-dimensional, validated and reliable patient questionnaire that evaluates and quantifies cancer quality of life across several dimensions (physical, functional emotional andsocial well being and well being). Patients respond to each item on a 5-point Likert-type scale ranging form 0 (not at all) to 4 (very much). On average, it requires less than 10 minutes to complete the questionnaire. An overall HRQoL score can be calculated, with higher scores reflecting better HRQoL. The FACT-G total score ranges from 0 (impaired quality of life) to 185 (unimpaired quality of life).

The Anti-A (FACT-Anti-A) subscale has 24 additional items and the FACT-ES 19 items. When all subscales are used in combination, four nausea, SOB, joint pain and diarrhoea are only asked to avoid overlap and double counting. Each subscale is an independently validated tools designed specifically for use with the FACT-G to assess the symptoms related to endocrine therapies (FACT-ES) and those of small molecule inhibitors (FACT-Anti-A). We will therefore cover most of the recognised main toxicities of fulvestrant, everolimus or AZD2014.

8.1.4 Pharmacokinetics

8.1.4.1 AZD2014

Patients on the AZD2014 arms at selected sites will have AZD2014 PK analysis performed. .

AZD2014 PK sampling times are as follows:

- Day 1, Cycle 1: 2ml of venous blood to be collected at 0.75-2h, 2.5–4h and 5–8h after taking AZD2014.
- Day 15, Cycle 1: 2ml of venous blood to be collected pre-dose immediately before taking AZD2014 and 1-3h and 5-8h after taking AZD2014.
    - For the continuous schedule, the Cycle 1 Day 15 samples should only be taken if the AZD2014 doses for the previous 3 days have all been taken as indicated.
    - For the intermittent schedule, the Cycle 1 Day 15 samples should only be taken if the AZD2014 dosing was started on day 14 (rather than day 15); if AZD2014 was only started on day 15, patients should come back on day 16 for their PK analysis.

The exact date and time of each PK sample and dose on each PK day must be recorded in the CRF. In addition for Cycle 1 Day 15 the exact date and time of the 2 doses immediately prior to the PK day must be recorded on the CRF. The bioanalysis of all PK samples will be performed by Covance

AZD2014 plasma concentrations and all other relevant associated data (e.g sampling and dosing time information) taken following the first AZD2014 dose and following multiple dosing will be merged with similar data from other studies in order to estimate appropriate AZD2014 PK parameters for each patient using non-linear mixed effects population modelling techniques.

PK parameters, where possible, will include plasma drug clearance (CL/F), estimated maximum drug concentration (Cmax), elimination half-life (t1/2) and volume of distribution (Vss/F). A covariate model (using demography parameters) will be added to the defined PK model. Modelling of the PK with pharmacodynamic endpoints, QTc, AEs and efficacy endpoints can then be undertaken as appropriate.

The results of any such analyses will be reported separately to the CSR for this study.

8.1.4.2 Fulvestrant

Patients on all arms at selected sites will have fulvestrant PK samples taken.

Fulvestrant PK sampling times are as follows:

- Day 1, Cycle 2: 3mL of venous blood to be collected pre-dose immediately prior to administration of the fulvestrant injection. Please be aware that 3mL of blood is being collected into a 4mL blood tube.
- Day 1, Cycle 3: 3mL of venous blood to be collected pre-dose immediately prior to administration of the fulvestrant injection. Please be aware that 3mL of blood is being collected into a 4mL blood tube.

The exact date and time of each PK sample and dose on each PK day must be recorded in the CRF. The bioanalysis of all PK samples will be performed by Covance.

Where possible the PK parameter Css_{min} will be determined for fulvestrant in each treatment arm from the pre-dose plasma samples taken just before the fulvestrant injections on Cycle 2 Day 1 and Cycle 3 Day 1.

These values will be compared to reported trough concentrations from patients receiving fulvestrant 500mg as a single agent in other studies. The results of any such analyses will be reported separately to the CSR for this study.

8.1.5 Biological specimen collection and assays

The collection of biological samples is an essential part of this study. All patients will be consneted for the collection and use of research blood and tissue samples. All samples will be linked anonymised and only identified by the trial ID and unique sample number allocated by the CECM MANTA team. These results may be reported separately from the clinical study report. Details on biological specimen collection, processing, storage and shipment are provided in the MANTA laboratory manual.

8.1.5.1 Required Archival Tissue Sample

To be eligible for this study, patients are required to have a representative formalin-fixed, paraffin-embedded (FFPE) tumour specimen that enables the definitive diagnosis ER-positive breast cancer, with adequate viable tumour cells in a tissue block.

- The minimum tissue size is 0.5 x 0.5 x 0.2 cm with ≥10% tumour content or 0.5 x 0.25 x 0.2 cm with ≥20% tumour content or 0.25 x 0.25 x 0.2 cm with ≥ 40% tumour content.
- Tumour blocks are preferred, but in the event that local regulations prevent the shipment of tumour blocks, 20 unstained, serially-cut 4-µm-thick slides are requested.

Multiple blocks, or blocks plus slides, can be combined to achieve the minimum requirements indicated. Cytological and fine-needle aspiration biopsy samples are not acceptable. The samples must be accompanied by an associated anonymised pathology report. If the archival tissue is either insufficient or unavailable, the patient will be required to give a fresh biopsy in order to still be eligible for the study. This sample must be obtained prior to randomisation. The associated anonymised pathology report must accompany the sample.

8.1.5.2 Optional Fresh Tissue Biopsy

Patients will be offered the opportunity to have additional tissue taken from the primary tumour or a metastatic lesion as part of the trial, during screening and at disease progression. Patients who have an initial biopsy taken can withdraw their consent for subsequent tissue and continue on the main part of the study. Analysis of this tissue will include genetic and molecular tests.

Wherever feasible, two biopsies should be obtained. The first biopsy should be placed immediately into 10% buffered formalin. The second biopsy is to be placed in sterile tubes and should be snap frozen immediately in liquid nitrogen or dry ice and stored frozen at ≤ -70°C.

The sample collection date, the exact time of collection, and the time of exposure to fixative (formalin) must be entered on the appropriate tumour tissue collection CRF page(s).

8.1.5.3 Blood sample collection

At specified timepoints, 2 blood samples (2 x 10 ml EDTA whole blood tubes, 2 x 2.5 ml PAXgene RNA tubes) are required for all consenting patients. Tubes will be labelled with site name, date of specimen, and patient study number. No personal identifiers (patient name, initials, or date of birth) will be placed on the tube or accompanying documentation.

8.1.5.4 Biosample Assay Methods

The multiple assays, described below, may be performed with the material derived from the 10-20 freshly cut unstained tumour slides collected from each patient as part of the eligibility for this study. It is likely that not all assays will be performed on samples provided by each patient (possibly because of insufficient tumour material or inadequate sample quality).

Exploratory outcome measures may include genome-wide measurements in tumour DNA and RNA, including mutational status, RNA gene-expression values, DNA copy number, metabonomics, and protein expression and phosphorylation. Exploratory analysis may include, but will not be limited to, the following:

- *Mutational analysis of PI3K:* Somatic mutations in the PIK3CA gene are found in approximately 35-40% of ER-positive breast cancers and occur most commonly in Exons 9 and 20 in the codons encoding amino acids E542, E545, and H1047. Real-time PCR (RT-PCR) assays that amplify exons that are commonly mutated in PIK3CA offer a sensitive and quantitative method to detect mutations from archival tumour material. DNA will be extracted from tumour samples and subjected to quantitative RT-PCR (qRT-PCR) assays that detect the wild-type allele as well as assays for nucleotide substitutions that may include but are not limited to the following amino acid changes: C420 (R), E542 (K), E545 (A/D/G/K), and H1047 (L/R/Y). Following histopathological review, samples with <20% tumour content will be enriched

for tumour content by macro- or microdissection.

PI3K mutational analysis might also be examined sequencing techniques. In addition to DNA extraction from tumour samples, cfDNA will be extracted from plasma samples collected from patients and will be used for the detection of oncogenic mutations.

- *PTEN Status:* PTEN status will be examined by IHC. Archival tumour material will be scored and a result reported only if appropriate staining is observed in internal control stromal or normal (non-tumour) tissue elements. PTEN null tumours are defined as those that exhibit no detectable PTEN immunostaining in neoplastic cells but do show at least moderate staining in surrounding non-tumour tissue as an internal control for sample handling.

  PTEN status may also be examined by qRT-PCR assay for mRNA levels or through a fluorescence in situ hybridization (FISH) assay for chromosomal loss.

- *Estrogen and Progesterone Receptor Status:* ER and PR status will be confirmed centrally using approved IHC assays in accordance with existing guidelines in an accredited laboratory. Tumours (from either primary or metastatic sites) must express ER or PR in ≥1% cells to be considered positive (Hammond et al. 2010). The results of this analysis will not be required to satisfy enrolment criteria and may not be available prior to patient randomisation. If the results from the central laboratory analysis suggest that a patient's tumour is ER-negative, the treating investigator will be informed of this result, and the patient's continued participation in the study will be at the discretion of the treating investigator.

- *HER2 Testing:* Tumour samples might also be tested centrally for confirmation of negative HER2 status by IHC through according to national guidelines. An IHC result of 3+ will be considered HER2 positive. An IHC result of 2+ will be considered ambiguous, and tissue will be tested for HER2 gene amplification. HER2 gene amplification will be assessed on archival primary tumour material through use of in-situ hybridisation (ISH) according to national guidelines. The results of this analysis will not be required to satisfy enrolment criteria and may not be available prior to patient randomisation. If the results from the central laboratory analysis suggest that a patient's tumour is HER2 positive (IHC3+ or ISH-positive) the treating investigator will be informed of this result, and the patient's continued participation in the study will be at the discretion of the treating investigator.

- *Additional Mutation Detection and Copy Number Analyses:* DNA obtained from FFPE sections may also be analyzed for mutations or copy number alterations in relevant oncogenes and tumour suppressor genes. Specifically, presence of activating Akt1 or PIK3R1 mutations or inactivating PTEN mutations will be determined using PCR (hotspot) and/or sequencing techniques in archival tissue specimens. These assays may also be performed on cfDNA if sufficient sample remains after running the PIK3CA mutation assay. qPCR-based copy number assays for c-MYC, CCND1, CDKN2A, FGFR1, FGFR2, IGF1R, PIK3CA, CDK4, and potentially other genes involved in PI3K signalling are planned on genomic DNA extracted from tumour samples. If sufficient DNA remains after the assays above have been performed, genome-wide methods for mutation detection and potentially DNA copy number profiling may be performed. Whole genome-amplified material will be used where necessary.

- *mRNA and miRNA Expression Profiling:* In cases where there is sufficient archival or fresh tissue to isolate RNA, gene expression analysis of a panel of genes important in breast cancer, PI3K signalling, and/or endocrine-therapy resistance will be performed. In the event that frozen tumour tissue is available, RNA will be extracted and profiled for global gene expression or miRNA levels through use of a validated commercially available platform. The goal will be to examine whether there are gene-expression patterns that are associated with clinical response.

- *Additional Immunohistochemistry Assays:* Ki67 protein levels will be determined by IHC through use of standard techniques, as a marker of the proliferative state of the tumour. If sufficient sections remain, IHC may also be performed for analytes such as INPP4B, pPRAS40, p4EB-P1, and pS6, because phosphorylation of these proteins may correlate with the pathway activation status in neoplastic cells

- *Reverse-Phase Protein Arrays;* Reverse-phase protein arrays offer the potential to profile hundreds of possible phosphorylation events in very small quantities of tumour material such as might be obtained from laser-capture microdissection from a biopsy or from archival frozen, non-FFPE tissue. The basis of the technology is to immobilize small amounts of lysate from a cell line or tumour sample in serial dilution on a microarray slide. Multiple samples are thus arrayed on a slide and can be probed with antibodies that detect a particular phosphoepitope. Using this technology, up to 100 key signalling nodes representing a number of pathways known to be dysregulated in breast cancer might be evaluated, including but not limited to receptors in the HER family and multiple components of PI3K/mTOR-, estrogen-, and RAS/MAPK-signalling pathways.

8.1.6 Chain of Custody

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 will keep full traceability of samples from receipt of arrival to further shipment or disposal (as appropriate).

In the event that a patient withdraws their consent from the study all samples and data collected up to that date will be used in the study but no further data will be collected. Queen Mary University of London as the Sponsor will keep overall oversight of the entire lifecycle through internal procedures and monitoring of study sites, the Chief Investigator will be the custodian of the samples. Samples will be transferred from participating sites to Barts Cancer Institute, Queen Mary University of London. Those retained for further ethically approved research will be registered with the Barts and the London Queen Mary's School of Medicine and Dentistry Tissue Bank (HTA Licensing number: 12199). Samples may be transferred to organisations (including commercial organisations) within or outside the EU for analysis.

8.2 Screening Assessments

Informed consent must be obtained before study-specific screening evaluations are performed and must be documented in the patient's medical chart.

After written informed consent has been obtained the study site will fax the patient's registration form to the coordinating centre prior to commencing screening. The study site will then obtain the patient's screening number from the coordinating centre..

Local laboratories will perform all laboratory evaluations. Details on biological specimen collection are provided in Section 8.1.5. Please see the Study Flowcharts provided in Section 8.6 for schedules of screening and pre-treatment assessments.

8.3 Assessments during Treatment

Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays. Please see the Study Flowchart provided in Section 8.6 and 8.7 for schedules of treatment period assessments and allowable deviations.

After the 3 initial doses of Fulvestrant (i.e. after Cycle 2 Day 1) Fulvestrant may be moved by up to 1 week forward or backwards to accommodate holidays, vacations, and unforeseen delays. AZD2014 or Everolimus should be taken according to schedule.

8.4 Treatment Completion Visit

Patients who are discontinued from study drug should return for a end of treatment visit. This visit should occur within 30 days after the last administration of the study medication.

Please see the Study Flowcharts provided in Section 8.6 and 8.7 for assessments to be performed at the end of treatment visit.

8.5 Post Progression and Treatment Switch Phase

All patients will be followed for survival and subsequent anti-cancer therapies unless the patient requests to be withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study treatment but not from follow-up, the study staff may use patient medical records to obtain information about subsequent anti-cancer therapies.

Switch to AZD2014 for patients treated with Fulvestrant + Everolimus

At the time of documented disease progression by RECIST1.1, patients randomised to receive fulvestrant + everolimus who still meet eligibility criteria (see Section 5.4. and 5.5.[4]) may be permitted to switch treatment with fulvestrant + AZD2014 (continuous daily schedule).

[4] With the exception of pre-treatment with everolimus and/or fulvestrant

Patients will receive switched therapy until progression, intolerable toxicity, elective withdrawal from the study, or until the completion or termination of the study, whichever occurs first. As with the main study fulvestrant + AZD2014 (continuous daily schedule arm), the AZD2014 dose will start on a dose of 50 mg BD. As with the main study fulvestrant + AZD2014 (continuous daily schedule arm), 50 mg BD is the maximum allowed dose of AZD2014. The dose level can be reduced in line with section 7.6.2. In the treatment switch phase unlike the main study fulvestrant + AZD2014 (continuous daily schedule arm), patients will not be administered Fulvestrant on day 15 of the first cycle.

Patients who undergo treatment switch will follow the assessments and procedures described in Section 8.7. The duration of each cycle will continue to be 28 days and the cycle numbers will "reset" to 1 and will be followed by the "X" suffix (e.g., Cycles 1X, 2X, etc.).

Treatment switch **must begin no later than 28 days** after the clinic visit at which progression is determined and the interval between the initiation of fulvestrant on Day 1 of Cycle 1X and the previous administration of fulvestrant must be ≥25 days. If the interval between the administration of the last dose of fulvestrant and the start of Day 1 of Cycle 1X is <25 days, then either of following two options is acceptable, at the investigator's discretion:

- Only open-label AZD2014 continuous daily schedule treatment is administered on Day 1 of Cycle 1X and the initiation of fulvestrant treatment in the treatment switch phase is delayed to Day 1 of Cycle 2X, or
- The start of Day 1 of Cycle 1X (and administration of fulvestrant in combination with open-label oral study drug treatment) is delayed until ≥25 days have elapsed since the prior administration of fulvestrant.

Patients must have adequate haematological and end-organ function, described in the Inclusion Criteria (Section 5.4.) prior to undergoing treatment switch based on assessments and procedures performed within 28 days prior to Day 1 of Cycle 1X.

Survival

Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, or study termination by the sponsor. All patients will be followed for survival information unless the patient requests to be withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study treatment but not from follow-up, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

Subsequent Anti-Cancer Therapies

All patients will be followed for subsequent endocrine therapies or treatment with PI3K, Akt or mTOR inhibitors. Information will be collected via telephone calls, patient medical records, and/or clinic visits every 3 months until death, loss to follow-up, or study termination by the TSC.

Ongoing Adverse Events

Patients with an unresolved adverse event or serious adverse event at treatment completion or study drug discontinuation will be contacted by the investigator or his or her designee to determine the status of the event until the event is resolved or stabilised, the patient is lost to follow up, or it has been determined that the study treatment or participation is not the cause of the event.

Ongoing Tumour Assessments in patients discontinuing without progression

If a patient discontinues therapy for reasons other than progression, she will be followed by regular CT assessments until objective disease progression as defined by RECIST 1.1, death or withdrawal of consent, whichever occurs first

8.6 Study Flowchart for patients in the randomised part

	Screening/ Baseline (within 30 days prior to randomisation unless otherwise indicated)	Day 1 of each cycle (Some day 1 procedures not required at every cycle – refer to relevant footnotes)	Day 15, cycle 1	After 8, 16 and 24 weeks of treatment and every 12 weeks thereafter (± 1 week) (Not all procedures listed below are required at each of these timepoints – refer to relevant footnotes for details)	After 8, 16, 24, (32 and 40) weeks of treatment and every 12 weeks thereafter (± 1 week)	End of Treatment [19]	Follow-up[20]
Informed consent	X						
Archival Tumour Tissue (Paraffin embedded)[1]	X						
Medical History[2]	X						
PRO[3]	X	X		X		X	
Physical examination	X			X		X	
Weight (with height at screening only)	X			X		X	
Vital signs[4]	X	X				X	
ECOG Performance Status	X	X				X	
Concomitant medications[5]	X	X				X	
Dosing compliance		X				X	
Adverse events	X	X				X	X[21]
Full blood count	X[6]	X[7]		(X)[6]		X[7]	
HbA1c and Lipid Panel[8]	X			X		X	
Serum Biochemistry[9]	X	X				X	
Triplicate 12-lead ECG[10]	X	X					
LVEF assessment[11]	X						
Tumour Assessments [12]	X				X	X	X
Bone scan[13]	X			(X)			
EDTA whole blood (10 ml tube)[14]		X		(X)		X	
PAXgene tube (2.5 ml tube)[15]		X					
AZD2014 PK (2 ml tube)[16]		(X)	(X)				
Fulvestrant PK (4 ml tube)[17]		(X)					
Fresh Tumour Biopsy (optional)[18]	(X)					X	
Survival and anti-cancer therapy follow-up							X

Table 10: Study Flowchart

[1] In the event that archival tumour tissue is not available, patient's will be required to be rebiopsied to enter onto the MANTA trial.

[2] Complete medical history including diagnosis of cancer, histology, prior antitumour treatment and outcome, medications and their indications.

[3] PRO assessments will be performed at screening, on day 1 of every cycle for the first 4 cycles, at 24 weeks, every 12 weeks thereafter and at the End of Treatment Visit.

[4] Includes heart rate, systolic and diastolic blood pressure, while patient is in a seated position.

[5] Concomitant medications (includes prescription medications and over-the-counter preparations) used by the patient from the time of providing written informed consent, during the study, and up to the end of treatment visit will be documented.

[6] Full blood count including hemoglobin, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelet count at screening and **if clinically indicated** at weeks 8, 16 24, and every 12 weeks thereafter (± 1 week). At screening only, INR and aPTT should also be determined to assess eligibility. Screeninig bloods to be performed **within 1 week prior to randomisation.**

[7] Full blood count including hemoglobin, WBC, ANC, and platelet count. Pre-dose laboratory samples may be drawn within 96 hours prior to study drug administration. Results must be reviewed prior to study drug administration.

[8] Only required for patients receiving AZD2014 and Everolimus. Fasting (≥4 hours) lipid profile should include total cholesterol, high-density lipoprotein, low-density lipoprotein and triglycerides. Pre-dose laboratory samples may be drawn within 96 hours prior to study drug administration; results don't have to be available prior to continuation of treatment. Screeninig bloods to be performed **within 1 week prior to randomisation.**

[9] Biochemistry including corrected Ca, Na, K, glucose, AST/ ALT, AP, bilirubin, creatinine, protein. Pre-dose laboratory samples may be drawn within 96 hours prior to study drug administration. At a minimum, results of the following tests must be reviewed prior to study drug administration: glucose, creatinine, Na, K, bilirubin, AP and AST or ALT. Patients receiving fulvestrant only do not need to fast prior to the collection of the serum or plasma chemistry sample. Patients receiving AZD2014 or Everolimus should have bloods taken in a fasted state (≥ 4 hours). At screening only, biochemistry should also include creatinine clearance (if clinically indicated) and Mg to assess eligibility. Screeninig bloods to be performed **within 1 week prior to randomisation** and in fasted state (≥ 4 hours) for all patients.

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[10] Triplicate 12-lead ECG measurements will be obtained and should be collected as three recordings in close succession over a period of not more than 2 minutes. To minimize variability in autonomic tone and heart rate, it is important that patients are resting quietly in a supine position for at least 5 minutes prior to every ECG collection. To be performed at screeninig, cycle 2 day 1 and day 1 of every second cycle thereafter (i.e. cycle 2, 4, 6, 8 etc.). ECG to be performed 1 – 2 hrs after AZD2014 or Everolimus administration. Serum potassium and calcium levels must be within normal limits before recording ECGs. ECGs are not required for patients on the fulvestrant only arm unless clinically indicated.

[11] In addition to the ECG, an ejection fraction is to be determined within 6 weeks prior to randomisation, using the ECHO or MUGA technology. Bidimensional echocardiography (ECHO) is the preferred modality because of the global technetium [Tc-99m] shortage (but MUGA can be used alternatively). The same method used at screening should be used throughout the study.

[12] Tumour assessments should be performed at screening, after 8, 16, 24, 32 and 40 weeks of treatment, every 12 weeks thereafter (+/-1 week), and when clinically indicated for all patients, including those with bone-only disease. This schedule is to be maintained and will not be shifted for treatment delays. Patients who discontinue study treatment for any reason other than disease progression will continue to undergo tumour-response evaluations until progressive disease or initiation of other anti-cancer therapy. Screening assessments must include CT scans of the chest, abdomen, and pelvis, with additional anatomy as clinically indicated by extent of disease. Subsequent tumour assessments should include CT scans of the chest and abdomen and other sites of disease. MRI scans may be substituted for CT scans but MRI of the chest may only be performed with approval from the Sponsor. Additional anatomy may be imaged at follow-up on suspicion of new lesions. For patients with ***bone-only disease not visible on the CT or MRI scans*** being performed as part of the tumour assessments, bone scans should be repeated every 12 weeks (+/-1 week for flexibility in the event of isotope shortage), and when clinically indicated. A documented standard-of-care tumour assessment performed within 30 days prior to randomisation may be used for the screening assessment provided it meets the above requirements. The same imaging method used at screening must be used throughout the study. Response assessments will be performed by the investigator, on the basis of physical examinations and imaging scans, through use of RECIST v1.1. If a patient discontinues therapy for reasons other than progression, she will be followed by regular CT assessments until she withdraws consent, or dies.

[13] An initial bone scan should be performed within 6 weeks prior to randomisation. Bone scans should only be repeated in the event of clinical suspicion of progression of existing bone lesions that cannot be visualised on CT or MRI, the development of new bone lesions or in the assessment of a CR, if any disease was evident at screening. For patients with **bone-only disease** not visible on the CT or MRI scans being performed as part of tumour assessments, a bone scan should be repeated every 12 weeks (+/-1 week) and when clinically indicated.

[14] Two tubes at each time point to be taken on day 1 of cycle 1 (prior to study medication), on day 1 of cycle 2 (prior to study medication), after 16 weeks and at progression.

[15] Two tubes at each time point to be taken on day 1 of cycles 1 and 2 prior to study medication and 2.5–4h after first dose

[16] Patients on the AZD2014 arms at selected sites will have AZD2014 PK samples taken. PK sampling times are as follows: (1) Day 1 of Cycle 1 only for the continuous and intermittent AZD2014 schedules: 2 ml of venous blood to be collected at 0.75–2h, 2.5–4h and 5–8h after taking AZD2014; (2) Day 15 cycle 1: 2 ml of blood to be collected pre-dose immediately before taking AZD2014 and 1-3h and 5-8h after taking AZD2014. For the continuous schedule the Cycle 1 Day 15 samples should only be taken if the AZD2014 doses for the previous 3 days have all been taken as indicated. For the intermittent schedule, the Cycle 1 Day 15 samples should only be taken if the AZD2014 dosing for that week was started on day 14 (rather than day 15); if AZD2014 was only started on day 15, patients should come back on day 16 for their PK sampling.

[17] Patients on all arms at selected sites will have fulvestrant PK samples taken. PK sampling times are as follows: Day 1, Cycles 2 and 3 only: 3ml of venous blood to be collected pre-dose immediately prior to administration of fulvestrant.

[18] Patients will be offered the opportunity to have additional tissue taken from the primary tumour or a metastatic lesion as part of the trial, during screening and at disease progression. Wherever feasible, two biopsies should be obtained. The first biopsy should be placed immediately into 10% buffered formalin. The second biopsy is to be placed in sterile tubes and

should be snap frozen immediately in liquid nitrogen or dry ice and stored frozen at ≤ -70C. The sample collection date, the exact time of collection, and the time of exposure to fixative (formalin) must be entered on the appropriate tumour tissue collection log CRF page(s).

[19] The end of treatment visit should occur within 30 days after last dose of study medication. For patients enrolled in any arm, the visit at which disease progression is recorded may serve as the end of treatment visit. Patients who undergo treatment switch should have the end of treatment visit assessments and procedures performed only after treatment on the treatment switch arm is discontinued.

[20] All patients will be followed for survival and subsequent anti-cancer therapies unless the patient requests to be withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study treatment but not from follow-up, the study staff may use patient medical records to obtain information about subsequent anti-cancer therapies. Survival and anti-cancer therapy information should be collected every 3 months until death, loss to follow-up, or study termination and recorded in the follow-up form of the CRF.

[21] Patients with an unresolved adverse event or serious adverse event at treatment completion or study drug discontinuation will be contacted by the investigator or his or her designee to determine the status of the event until the event is resolved or stabilized, the patient is lost to follow up, or it has been determined that the study treatment or participation is not the cause of the event.

8.7 Study Flowchart for patients who undergo treatment switch

	Day 1, Cycle 1X [1]	Day 1 of each sub-sequent cycle (Some day 1 procedures not required at every cycle – refer to relevant footnotes)	Day 15, cycle 1	After 8, 16 and 24 weeks of treatment and every 12 weeks thereafter (± 1 week) (Not all procedures listed below are required at each of these timepoints – refer to relevant footnotes for details)	After 8, 16, 24, (32 and 40) weeks of treatment and every 12 weeks thereafter (± 1 week)	End of Treat-ment [15]	Follow-up[16]
PRO [2]	X	X		X		X	
Physical examination	X			X		X	
Weight	X			X		X	
Vital signs [3]	X			X		X	
ECOG Performance Status	X	X				X	
Concomitant medications [4]	X	X				X	
Dosing compliance		X				X	
Adverse events	X	X				X	X[17]
Full blood count	X[5]	X[6]		X[5]		X[6]	
Serum Biochemistry [7]	X	X				X	
HbA1c and Lipid Panel [8]	X[11]			X		X	
Triplicate 12-lead ECG [9]	X[11]	X					
Tumour Assessments [10]	X[11]				X	X	X
Bone scan [12]				(X)			
EDTA whole blood (10 ml tube) [13]		(X)				X	
PAXgene tube (2.5 ml tube) [14]		(X)					
Survival and anti-cancer therapy follow-up							X

Table 11: Study Flowchart for patients who undergo treatment switch

1 Treatment switch must begin no later than 28 days after the clinic visit at which progression is determined. If the interval between the administration of the last dose of fulvestrant and the start of Day 1 of Cycle 1X is <25 days then, at the investigator's discretion, either the start of Day 1 Cycle 1X is delayed or fulvestrant treatment in the treatment switch phase is delayed to Day 1 of Cycle 2X (see Section 8.5.)

2 PRO assessments will be administered at the start of the visit and on day 1 of every cycle for the first 4 cycles, at 24 weeks, every 12 weeks thereafter and at the End of Treatment Visit.

3 Includes heart rate, systolic and diastolic blood pressure, while patient is in a seated position

4 Concomitant medications (includes prescription medications and over-the-counter preparations) used by the patient from the time of providing written informed consent, during the study, and up to the end of treatment visit will be documented.

5 Full blood count including hemoglobin, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelet count at screening and **if clinically indicated** at weeks 8, 16 and 24, and every 12 weeks thereafter (± 1 week).

6 Full blood count including hemoglobin, WBC, ANC, and platelet count. Pre-dose laboratory samples may be drawn within 96 hours prior to study drug administration. Results must be reviewed prior to study drug administration

7 Biochemistry including corrected Ca Na, K, glucose, AST/ ALT, AP, bilirubin, creatinine, protein. Pre-dose laboratory samples may be drawn within 96 hours prior to study drug administration. At a minimum, results of the following tests must be reviewed prior to study drug administration: glucose, creatinine, Na, K, bilirubin, AP and AST or ALT. Patients receiving

fulvestrant only do not need to fast prior to the collection of the serum or plasma chemistry sample. Patients receiving AZD2014 should have bloods taken in a fasted state (≥ 4 hours).

[8] Fasting (≥4 hours) lipid profile should include total cholesterol, high-density lipoprotein, low-density lipoprotein and triglycerides, Pre-dose laboratory samples may be drawn within 96 hours prior to study drug administration; results don't have to be available prior to continuation of treatment.

[9] Triplicate 12-lead ECG measurements will be obtained and should be collected as three recordings in close succession over a period of not more than 2 minutes. To minimize variability in autonomic tone and heart rate, it is important that patients are resting quietly in a supine position for at least 5 minutes prior to every ECG collection. To be performed within 28 days prior to Day 1 of Cycle 1X, at cycle 2 day 1 and day 1 of every second cycle thereafter (i.e. cycle 2, 4, 6, 8 etc.). ECG to be performed 1 – 2 hrs after AZD2014 administration. ECGs are not required for patients who discontinue AZD2014 and continue on fulvestrant alone unless clinically indicated. Serum potassium and calcium levels must be within normal limits before recording ECGs.

[10] Tumour assessments should be performed within 28 days prior to Day 1 of Cycle 1X, after 8, 16, and 24 weeks of treatment and every 12 weeks thereafter (+/-1 week), and when clinically indicated for all patients including those with bone-only disease. This schedule is to be maintained and will not be shifted for treatment delays. Patients who discontinue study treatment for any reason other than disease progression will continue to undergo tumour-response evaluations until progressive disease or initiation of other anti-cancer therapy. Screening assessments must include CT scans of the chest, abdomen, and pelvis, with additional anatomy as clinically indicated by extent of disease. Subsequent tumour assessments should include CT scans of the chest and abdomen and other sites of disease. MRI scans may be substituted for CT scans but MRI of the chest may only be performed with approval from the Sponsor. Additional anatomy may be imaged at follow-up on suspicion of new lesions. For patients with ***bone-only disease not visible on the CT or MRI scans*** being performed as part of the tumour assessments, bone scans should be repeated every 12 weeks (+/-1 week for flexibility in the event of isotope shortage), and when clinically indicated. The same imaging method used at screening must be used throughout the study. Response assessments will be performed by the investigator, on the basis of physical examinations and imaging scans, through use of RECIST v1.1. If a patient discontinues therapy for reasons other than progression, she will be followed by regular CT assessments until she withdraws consent or dies

[11] These assessments do not need to be performed on Day 1 of Cycle 1X if performed within 28 days prior to Day 1 of Cycle 1X.

[12] An initial bone scan should have been performed within 6 weeks prior to randomisation to the initial treatment phase and does not need to repeated prior to commencing the treatment switch phase unless clinically indicated. Bone scans should only be repeated in the event of clinical suspicion of progression of existing bone lesions that cannot be visualised on CT or MRI, the development of new bone lesions or in the assessment of a CR, if any disease was evident at screening. For patients with **bone-only disease** not visible on the CT or MRI scans being performed as part of tumour assessments, a bone scan should be repeated every 12 weeks (+/-1 week) and when clinically indicated.

[13] Two tubes at each time point to be taken on day 1 of cycle 1X (prior to study medication), on day 1 of cycle 2X (prior to study medication), after 16 weeks and at progression.

[14] Two tubes at each time point to be taken on day 1 of cycles 1X and 2X prior to study medication and 2.5–4h after first dose.

[15] The end of treatment visit should occur within 30 days after last dose of study medication. The visit at which disease progression is recorded may serve as the end of treatment visit.

[16] All patients will be followed for survival and subsequent anti-cancer therapies unless the patient requests to be withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study treatment but not from follow-up, the study staff may use patient medical records to obtain information about subsequent anti-cancer therapies. Survival and anti-cancer therapy information should be collected every 3 months until death, loss to follow-up, or study termination and recorded in the follow-up form of the CRF.

[17] Patients with an unresolved adverse event or serious adverse event at treatment completion or study drug discontinuation will be contacted by the investigator or his or her designee to determine the status of the event until the event is resolved or stabilized, the patient is lost to follow up, or it has been determined that the study treatment or participation is not the cause of the event.

9 ASSESMENT OF SAFETY

9.1 Safety Parameters and Definitions

Safety assessments will consist of monitoring and recording protocol-defined adverse events (AEs) and serious adverse events (SAEs); measurement of protocol-specified haematology, clinical chemistry, coagulation variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drugs.

The Trial Sponsor or its designee is responsible for reporting relevant SAEs to the Competent Authority (CA), other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

The Sponsor, or its delegated designee, is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drug to the regulatory agencies and competent authorities by telephone or fax within 7 calendar days after being notified of the event. The Sponsor, or its delegated designee, will report other

relevant SAEs associated with the use of the study medication to the appropriate competent authorities (according to local guidelines), investigators, and EC by a written safety report within 15 calendar days of notification.

9.1.1 Adverse event (AE) and adverse reaction (AR)

An **adverse event** (AE) is any unfavourable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product or other protocol-imposed intervention, regardless of attribution. This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with breast cancer that were not present prior to the AE reporting period (see Section 9.2.1)
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies)
- AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention (e.g. invasive procedures such as biopsies, medication, or no treatment run-in).
- Pre-existing medical conditions (other than breast cancer) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

An **adverse reaction (AR)** is any untoward and unintended responses to an **IMP related** to any dose administered. All AE's judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

9.1.2 Serious adverse event (SAE) and serious adverse reaction (SAR)

A **serious adverse event** (SAE) is any AE regardless of causality that:

- Results in death (during treatment with, and for 30 days after stopping, study drug),
- Is life-threatening [5],
- Requires hospitalisation or prolongs existing hospitalisation [6],
- Results in persistent or significant disability or incapacity,
- Is a congenital anomaly/birth defect, or
- Requires medical intervention to prevent permanent damage, or other medically important event [7]

A Serious adverse reaction (SAR) is defined as a SAE that has a definite, probable or possible causal relationship to the study drugs (Fulvestrant and/or AZD2014/everolimus).

All AEs that do not meet any of the criteria for serious, should be regarded as non-serious AEs.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain) and will be graded using the NCI CTCAE, v4.03 scale; the event itself may be of relatively minor medical significance (such as severe headache). "Serious" is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient's life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations. Severity and seriousness should be independently assessed when recording AEs and SAEs on the CRF

9.1.3 Unexpected adverse event

An adverse reaction is 'unexpected' if its nature and severity are not consistent with the information about the medicinal product in question set out:

- In the case of a product with a marketing authorization, in the summary of product characteristics for that product;

[5] Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.

[6] Hospitalisation admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry or elective operations are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).

[7] An important medical event is an event that may not result in death, be life-threatening, or require hospitalisation but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs.

- In the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.

Many adverse events that occur in this study, whether they are serious or not, will be known treatment related toxicities due to Fulvestrant or AZD2014/everolimus. For this trial all SAEs independent of attribution and expectedness should be reported on the SAE/SAR form. Expected events are listed in section 5.4 of the Investigator's Brochure (IB) for AZD2014, section 4.8 of the Summary of Product Characteristics (SmPC) for Everolimus (Afinitor) and section 4.8 of the SmPC for Fulvestrant (Faslodex).

9.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

SUSAR is a Serious Adverse Reaction (SAR) the nature or severity of which is not consistent with the applicable product information (i.e. Investigator's Brochure or SmPC).

9.2 Methods and Timing for capturing and assessing safety parameters

The investigator is responsible for ensuring that all AEs and SAEs (as defined in Section 9.1) are recorded on the CRF and reported to the CECM in accordance with protocol instructions.

9.2.1 Adverse Event Reporting Period

After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be recorded (e.g., SAEs related to invasive procedures such as biopsies, medication, or no treatment run-in).

After initiation of study medications, all AEs and SAEs regardless of attribution will be recorded until 30 days following the last administration of study treatment or study discontinuation/termination, whichever is later. After this period, investigators should report only SAEs that are believed to be related to prior study treatment.

9.2.2 Assessment of Severity and Causality of Adverse Events

Investigators will seek information on AEs and SAEs at each patient contact. All AEs and SAEs, whether reported by the patient or noted by authorized study personnel, will be recorded in the patient's medical record and on the Adverse Event CRF.

For each AE and SAE recorded on the applicable CRF, the investigator will make an assessment of seriousness (see Section 9.1.2 for seriousness criteria), severity, and causality.

provides guidance for grading AE severity, and provides guidance for assessing the causal relationship to the investigational product(s).

The AE grading (severity) scale found in the NCI CTCAE, v4.03, will be used for AE reporting. The alternative definitions for Grade 1, 2, 3, and 4 events (Table 12) should be used when the observed or reported AE is not in the NCI CTCAE listing.

Grade	Severity	Alternative Description
1	Mild	Awareness of sign or symptom, but easily tolerated; Transient or mild discomfort (<48 hours); no interference with the patient's daily activities; no medical intervention/therapy required
2	Moderate	Discomfort enough to cause mild to moderate interference with normal daily activities; No or minimal medical intervention/therapy required.
3	Severe	Considerable interference with the patient's daily activities; medical intervention/therapy required; hospitalisation possible
4	Very severe, life threatening or disabling	Extreme limitation in activity; significant medical intervention/therapy required, hospitalisation probable
5	Death related to AE	

Table 12: Adverse Event Grading (Severity) Scale

To ensure consistency of causality assessments, investigators should apply the following general guidelines:

Is the AE/SAE suspected to be caused by the investigational product based on facts, evidence, science-based rationales, and clinical judgment?	
Yes	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the AE/SAE.
No	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the AE/SAE.

Table 13: Causal Attribution Guidance

The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the "Yes" or "No" causality assessment for individual AE reports, the CI will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.

9.3 Procedures for Recording Adverse Events

All AEs, whether expected or not, should be recorded in the relevant section of the CRF. The trial centre will report all adverse events and adverse reactions to the competent authorities and the EC in accordance with their guidelines. Reporting to non-UK competent authorities and ECs will be carried out by the respective National Coordinating Centre (NCC). Any questions concerning adverse event reporting should be directed to the Trials Office in the first instance.

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the CRF. Avoid colloquialisms and abbreviations. There is one CRF for recording AEs or SAEs. Only one medical concept should be recorded in the event field on the Adverse Event CRF.

9.3.1 Diagnosis versus Signs and Symptoms

If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases).

However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If an SAE, each individual event should be reported on a separate form. If a diagnosis is subsequently established, it should be reported as follow-up information.

9.3.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhoea is known to have resulted in dehydration, it is sufficient to record only diarrhoea as an AE or SAE on the CRF.

However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal haemorrhage leads to renal failure, both events should be recorded separately on the CRF.

9.3.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between patient evaluation time points. Such events should only be recorded once in the CRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded again on the Adverse Event CRF.

A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded on the Adverse Event CRF.

9.3.4 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (e.g., abnormalities that require study drug to be held or discontinued, more frequent follow-up assessments, further diagnostic investigation, etc.). If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x the ULN associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or aetiology changes.

9.3.5 Deaths

Deaths that occur during the protocol-specified AE reporting period (see Section 9.2.1) that are attributed by the investigator solely to progression of breast cancer will be recorded on the End of Treatment CRF and do not require immediate reporting to the CECM. All other on-study deaths, regardless of attribution, will be recorded on the Adverse Event CRF and have to be reported as an SAE to the CECM within 24 hours of becoming aware of the event.

When recording a death on the CRF, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, record “Unexplained Death” on the CRF.

During post-study survival follow-up, deaths attributed to progression of breast cancer will be recorded only on the Follow-up CRF.

9.3.6 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be recorded on the Medical and Surgical History CRF. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study.

When recording such events on the Adverse Event CRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

9.3.7 Worsening/ Progression of Breast Cancer

Worsening and/or progression of breast cancer (or events attributed thereto) should not be recorded as an AE or SAE. These data will be captured as efficacy assessment data only.

9.3.8 Hospitalisation, Prolonged Hospitalisation, or Surgery

Any AE that results in hospitalisation or prolonged hospitalisation should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalisation scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include a planned hospitalisation or prolonged hospitalisation such as the following:

- Hospitalisation or prolonged hospitalisation for diagnostic or elective surgical procedures for pre-existing conditions (including definitive surgery for breast cancer)
- Hospitalisation or prolonged hospitalisation required to allow efficacy measurement for the study
- Hospitalisation or prolonged hospitalisation for scheduled therapy of the target disease of the study

9.4 Expedited reporting requirements for serious adverse events (SAEs)

9.4.1 Fatal/Life-Threatening SAEs Related to Investigational Product

Any life-threatening (i.e., imminent risk of death) or fatal AE that is attributed by the investigator to the investigational product will be telephoned to the **MANTA Clinical Trial Coordinator** at the Centre for Experimental Cancer Medicine (CECM), Barts Cancer Institute, Queen Mary University of London, followed by submission of written case details on the SAE reporting form immediately as described in Section 9.4.2.The causality of the event should be assigned by the responsible investigator.

MANTA Clinical Trial Coordinator
Centre for Experimental Cancer Medicine (CECM)
Barts Cancer Institute, Queen Mary University of London
Old Anatomy Building, Charterhouse Square
London EC1M 6BQ
Tel: +44 (0) 20 7882 8503
Fax: +44 (0) 20 7882 8409

9.4.2 Reporting Requirements for all SAEs

SAEs and SARs should be reported from the time of randomisation and up to 30 days following the last dose of fulvestrant and/or AZD2014/everolimus. Details on SAE reporting are provided in Figure 6.

For all sites, investigators will submit reports of all SAEs, regardless of attribution, to the CECM (or its designee) immediately, for review by the CI. For initial SAE reports, investigators should record all case details that can be gathered on the SAE reporting form and fax to the CECM on the number below.

To report an SAE or SUSAR, an SAE form must be completed and faxed to the trials group within 24 hours of the clinician becoming aware of the event.

MANTA Clinical Trial Coordinator
Centre for Experimental Cancer Medicine (CECM)
Barts Cancer Institute, Queen Mary University of London
Old Anatomy Building, Charterhouse Square
London EC1M 6BQ
Tel: +44 (0) 20 7882 8503
Fax: +44 (0) 20 7882 8409

Please note, all adverse reactions or adverse events (whether or not they are SAEs or SUSARs) should also be recorded in the relevant sections of the case report.

Relevant follow-up information should be submitted to the CECM (or its designee) as soon as it becomes available and/or upon request. The CECM will share all information on SAEs with Astra Zeneca's Drug Safety Department.

All SAEs will be reviewed by the Chief Investigator (or designated representative) for causality and expectedness. Centres should respond as soon as possible to requests from the CI or designated representative (via the CECM) for further information that may be required for final assessment.

9.4.3 Expedited Reporting of SUSARs

If an SAE is defined as a SUSAR and is fatal or life threatening, the sponsor or designee will report this to the Competent Authority (and other regulatory bodies if applicable), and to the EC (if applicable) within 7 days of being notified of the event. Reporting to non-UK competent authorities and ECs will be carried out by the respective NCC.

If an SAE is defined as a SUSAR and is not fatal or life threatening, sponsor or designee will report this to the Competent Authority (and other regulatory bodies if applicable) , and the EC within 15 days of being notified of the event. Reporting to non-UK competent authorities and ECs will be carried out by the respective NCC.

Day zero for SUSAR reporting is the day the CI (CECM) receives a medically assessed SAE report.

The Principal Investigator at all actively recruiting centres will be informed of any SUSARs occurring within the trial.

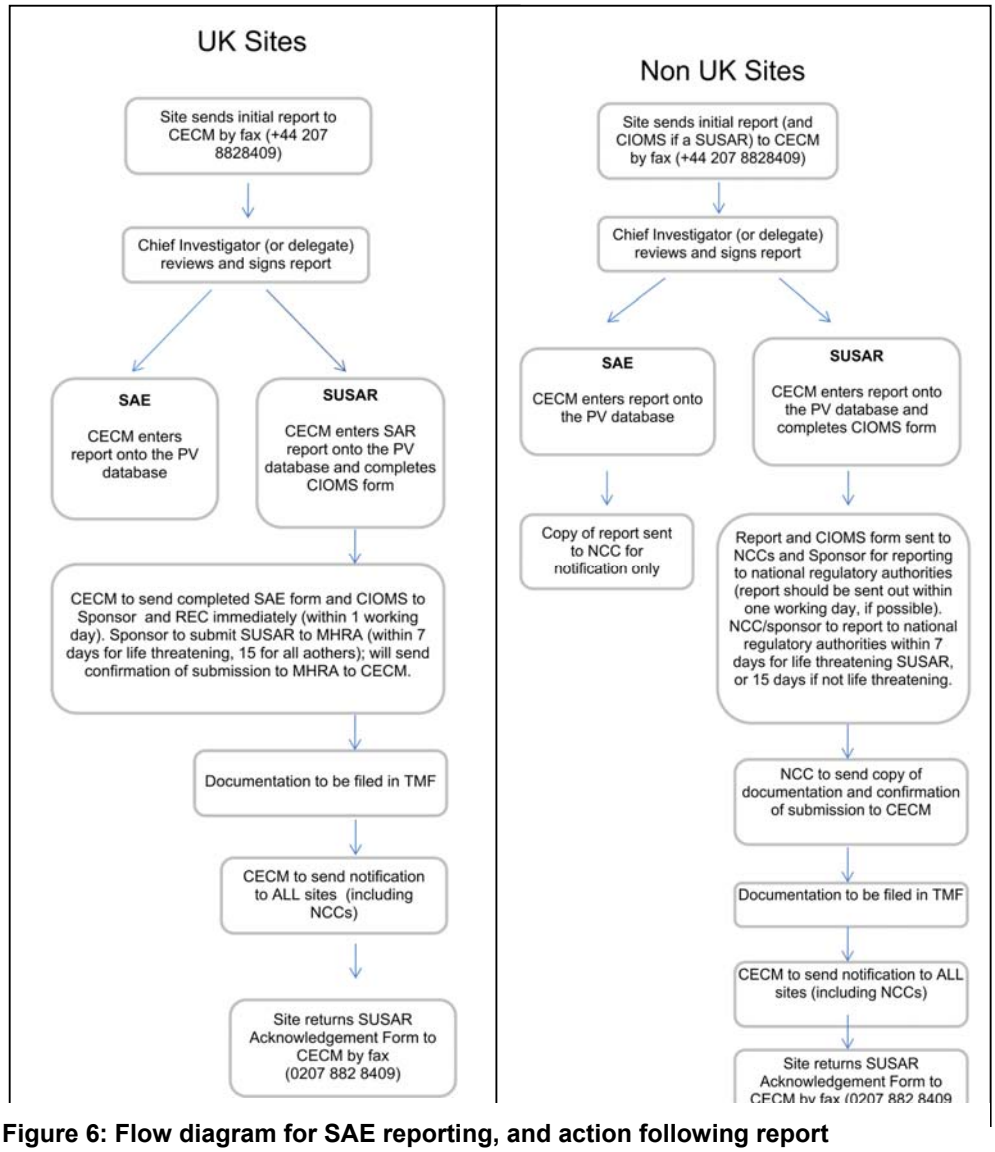

Figure 6: Flow diagram for SAE reporting, and action following report

9.5 Follow-up of SAEs

Information on outcome of the SAE which may not be available at the time the SAE was initially reported should be completed on the follow-up SAE form within 15 days of the initial report of the event and submitted to CECM. However, centres should continue to send follow up of SAEs until clinical recovery is complete and laboratory results have returned to normal, or until disease has stabilised

9.5.1 Annual Reporting of Serious Adverse Reactions

An annual report will be provided to the competent authorities (and other regulatory authorites if applicable) and the EC at the end of the reporting year. This will be defined as the anniversary of the date when the Clinical Trials Authorisation (CTA) was obtained. The annual report will include all related events reported on SAE/SAR forms).

9.6 Type and duration of follow-up of patients after adverse events

Patients with an unresolved AE or SAE will be followed by the investigator until the event is resolved or stabilised, the patient is lost to follow up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the Adverse Event CRFs and in the patient's medical record to facilitate source data verification (SDV).

For some SAEs, the Sponsor or its designee) may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

9.7 Post Study Adverse Events

At the last scheduled visit, the investigator should instruct each patient to report to the investigator any subsequent SAEs that the patient's personal physician believes could be related to prior study treatment. The investigator should notify the CECM of any death or other SAE occurring at any time after a patient has discontinued or terminated study participation if believed to be related to prior study treatment. The CECM should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient who participated in this study. The investigator should report these events to the CECM on the study CRF. If the study CRF is no longer available, the investigator should report the event directly to the CECM by telephone.

10 STATISTICAL PROCEDURES

10.1 Analysis of the Conduct of the Study

The number of patients who are randomised will be tabulated by study site and treatment arm. Eligibility exceptions and protocol deviations will be summarised by treatment arm. Patient disposition will be tabulated by treatment arm, and reasons for premature discontinuation will be summarised in tables and as a CONSORT flow chart.

10.2 Populations for analysis

All efficacy analyses will be performed on an intent-to-treat basis. The primary efficacy analysis will be based on local imaging review at participating centres. In addition, all scans will also be subjected to a central review process which will be the basis for a secondary efficacy analysis. Primary and secondary efficacy analyses will include all randomised patients, with patients analyzed according to the treatment arm to which they were randomised. The secondary efficacy analyses relating to ORR and CB will however be according to the treatment that patients received.

The safety analysis will be conducted on all patients who received at least one dose of the study treatment with patients analysed according to the treatment they actually received. Efficacy and Safety analyses will include additional patients recruited to the three-arm version of the trial. Efficacy analyses will be repeated including just those patients in the four-arm part of the study to see the sensitivity.

10.3 Analysis of Treatment Group Comparability

Demographic and baseline characteristics (e.g., age, tumour size) and stratification factors will be summarised using mean, standard deviation, median, and range for continuous variables, and proportion for categorical variables, as appropriate. Confidence intervals will be calculated as appropriate. Summaries will be presented overall and by treatment arm. The baseline value of any variable will be defined as the last available value prior to the first administration of study treatment.

10.4 Efficacy Analysis

The primary comparison will be between fulvestrant + AZD2014 (continuous daily schedule) relative to fulvestrant alone. Any comparison with fulvestrant + everolimus or with intermittent dosing of AZD2014 will be secondary. No adjustment for multiple comparisons will be done for secondary efficacy analyses.

Sensitivity analysis

The efficacy endpoints will be analysed according to ITT analysis based on all patients (including the additional patients from the three-arm version of the trial). Sensitivity analysis will be carried out by seperately analysing those patients in the four-arm part of the study. Safety analyses will include all recruited patients.

10.4.1 Primary Efficacy Endpoint

Kaplan–Meier methodology will be used to estimate the median PFS for each treatment arm. PFS is defined as the time from randomisation to disease progression or relapse (using RECIST, Version 1.1) or death on study from any cause, whichever occurs first. For patients who have not died or experienced disease progression at the end of study, PFS will be censored on the last date the patient was known to be progression free.

For patients with measurable disease at baseline, progression will be determined according to the RECIST criteria (see Post-text supplement 1). **In the absence of measurable disease at baseline**, patients with bone only lesions, lytic or mixed (lytic + sclerotic), will be allowed to enter the study and the following will be considered disease progression among these patients:

- The appearance of one or more new lytic lesions in bone
- The appearance of one or more new lesions outside of bone
- Unequivocal progression of existing bone lesions

Note: Pathologic fracture, new compression fracture, or complications of bone metastases will not be considered as evidence of disease progression, unless one of the above-mentioned criteria is fulfilled.

Separate analyses of PFS will be performed based on IRF and investigator assessment. The primary efficacy analysis will be based on investigator assessment. A secondary PFS analysis will use the IRF data.PFS will be assessed in all patients and separately within the PI3K-pathway activation subgroup of patients (defined as patients with activating PIK3CA mutations). The stratified log-rank test stratified by baseline stratification factors will be used as the primary analysis for treatment comparison. The effect of treatment will be estimated by the HR together with its corresponding 95% CI and p-value. The log-rank method to be used to estimate the HR is that in Freedman (1982) and Schoenfield (1981). The proportional hazards assumption will be examined using Schoenfield residuals. Statistical assumptions will be assessed and additional analyses may be considered if these assumptions do not hold.

10.4.2 Secondary Efficacy Endpoints

Objective response

RECIST 1.1 criteria will be used to assess response. Objective response will be calculated in patients with measurable disease at baseline. Patients without measurable disease at baseline will not be included in this analysis. Patients without a post-baseline tumour assessment will be considered to be non-responders. An estimate of the objective response rate and 95% CIs (Clopper and Pearson 1934) will be calculated for each treatment arm. CIs for the difference in tumour response rate (Satner and Snell 1980; Berger and Boos 1994) will be calculated. The relative risk of response (treatment:control) will be reported along with the associated 95% confidence interval based on logistic regresion model.

Separate analyses of objective response will be performed based on IRF and investigator assessment

Change in tumour size at 16 weeks

For patients with measurable disease at baseline, change in tumour size at 16 weeks is based on RECIST measurements taken at baseline and at week 16. Tumour size is the sum of the longest diameters of the target lesions (TL) that have been selected at baseline. Baseline for RECIST is defined to be the last evaluable assessment prior to starting treatment. The change in tumour size will be assessed using the log (ratio) of the week 16 tumour size over the baseline tumour size for each patient. More details on TLs selection and assessment during the treatment can be found in Appendix 3 of the protocol.

For patients who progress before week 8, a tumour assessment should be conducted and recorded at the time of progression. The tumour size from the progression assessment will be used instead of the week 8 assessment for these patients.

Patients who discontinue study treatment (prior to 16 weeks) for reasons other than objective disease progression should have tumour assessments scans performed as scheduled in the protocol and the tumour size from the week 8 or 16 assessment will be used in this analysis.

Whenever tumour size data for the week 16 assessment is available then this should be used in the analysis of change in tumour size at 16 weeks. A windowing rule will be applied and will follow the protocol allowed visit window; therefore, any RECIST scan performed within ± 1week of the protocol scheduled visit will be used for the week 16 visit. If a patient has an incomplete week 16 assessment then provided ≤ 1/3 of the lesions sizes are missing, the sum of diameters at week 16 can be estimated by scaling-up (based on the baseline sizes) to give an estimated sum of diameters and this will be used in calculations (this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the baseline sum of diameters excluding the lesions that are missing and determining at what rate the lesions are changing). This estimated sum of diameters will be used in the analyses to estimate change in tumour size at 16 weeks.

If a patient does not undergo a valid week 16 assessment (i.e. sum of diameters at week 16) is unknown or cannot be estimated) then imputation rules will apply which will be based on estimating patients week 16 change in tumour size given other post baseline measurements are available and fitting linear regression models for each patient.

The distribution of the tumour size measurement data will be assessed without knowledge of the randomised treatment assignment. If the week 16 changes in tumour size data follow a log-normal distribution, these data will be analysed as described previously. If, however, it is judged the data do not adequately follow a log-normal distribution then the use of untransformed percentage changes or a non-parametric approach could replace the log transformed analysis as the primary approach.

Change in tumour size at week 16 (or progression if prior to week 16) will be assessed in all patients and separately within the subgroup of patients with aberrant PI3K-pathway activation. Change in tumour size will be assessed as the log of the ratio of week 16 tumour size over the baseline tumour size measurement for each patient as these data have been assumed to be log-normally distributed. The effect of AZD2014 on change in tumour size will be estimated in the overall population and also within the PI3K-pathway activated subgroup from analysis of covariance (ANCOVA) models including covariates for treatment, baseline tumour size (log transformed) and PI3K-pathway activation. If the week 16 tumour size is 0, this will be imputed as 0.01 in the log transformed analysis of these data.

The results of the analysis will be exponentiated and presented in terms of adjusted geometric least squares means (glsmeans) for each treatment, together with their 2-sided 80% confidence intervals. Estimates of the treatment effect (ratio of glsmeans, AZD2014[8] + fulvestrant: fulvestrant, or AZD2014 + fulvestrant: everolimus + fulvestrant) will be calculated, together with their 2-sided 80% confidence intervals. The adjusted glsmeans and ratio of glsmeans along with their associated confidence intervals may be back-transformed to % changes from baseline by subtracting 1 and multiplying by 100 for ease of interpretation, as required.

Separate analyses of change in tumour size at 16 weeks will be performed based on IRF and investigator assessment

Clinical Benefit rate

Clinical Benefit rate is defined as number of patients with complete or partial response or stable disease maintained ≥24 weeks (as assessed by the site radiologist and/or investigator, using RECIST1.1) divided by the number of patients in the analysis. Patients without a post-baseline tumor assessment will be considered to have no clinical benefit. An estimate of the clinical benefit rate and 95% CIs (Clopper and Pearson 1934) will be calculated for each treatment arm. CIs for the difference in clinical benefit rate (Satner and Snell 1980; Berger and Boos 1994) will be calculated. The relative risk (treatment:control) will be reported along with the associated 95% confidence interval based on logistic regresion model.

[8] Separate analyses for continuous and intermittent AZD2014 schedules

Separate analyses of objective response will be performed based on IRF and investigator assessment

Duration of Objective Response or Clinical benefit

For patients with an objective response, duration of objective response is defined as the time from initial complete or partial response to disease progression or death on study from any cause, whichever occurs first.

For patients with a clinical benefit (objective response or stable disease maintained ≥24 weeks), duration of clinical benefit is defined as the time from randomisation to disease progression or death on study from any cause, whichever occurs first.

Methods for handling censoring and for analysis are the same as those described for PFS.

Separate analyses of duration of objective response and duration of clinical benefit will be performed based on IRF and investigator assessment.

Summary statistics will be obtained; median duration might be compared between the treatment arms using the methodology described by Ellis et al [55],

Overall Survival

Overall survival is defined as the time from randomisation to death from any cause. All deaths will be included, whether they occur on study or following treatment discontinuation. For patients who have not died, overall survival will be censored at the date of last contact. Analysis methods are the same as those described for PFS.

10.5 Safety Analysis

Safety will be assessed through summaries of adverse events, laboratory test results, and changes in vital signs by treatment arm. Safety analyses will include all patients who receive any amount of study treatment. Safety data will be reported separately for each treatment group. The worst toxicity during each cycle and the worst toxicity during the entire treatment will be determined separately for each patient according to the criteria specified above.

Vital signs, temperature, weight and ECOG performance status data will be listed or summarised by treatment arm, study site, patient ID number, and scheduled measurement time.

Laboratory data will be tabulated by treatment arm, with values outside normal ranges identified and summarised by NCI CTCAE (Version 4.03) grade.

Verbatim descriptions of treatment-emergent adverse events will be mapped to the appropriate thesaurus terms and summarised by mapped term, appropriate thesaurus level, and NCI CTCAE grade. For each patient's adverse event, the maximum severity reported will be used in the summaries. Serious adverse events, including deaths, will be summarized separately.

Exposure data will be summarised by treatment arm, indicating total exposure to study drug and total time on study, as well as the number of any dose interruptions or reductions.

10.6 Calculation or derivation of patient-reported outcomes

To reduce missing data, the FACT-G -Anti-A and ES assessment questionnaires will be administered by the centres before the patient sees the physician at baseline (screening), and thereafter sent by post by the co-ordinating centre for completion on Day 1 of every cycle for the first 4 cycles, at 24 weeks, every 12 weeks thereafter and at the End of Treatment Visit.

There are very clear imputation rules for calculation of FACT scores in the FACIT Handbook.

The primary endpoint will be a Trial Outcome Index (TOI) comprised of physical, functional, breast, anti-A and endocrine symptom subscale scores).

Secondary endpoints will be:

- An overall HRQOL score from the total FACT-G-AA-ES scales.
- Individual subscale scores from the 7 subscales. Individual items of most interest will also be pre-specified and analysed.

QOL data analysis will be mainly descriptive in nature looking at summary statistics, plots of profile over time. Also symptom improvement rates and time to deterioration will be summarised.

10.7 Pharmacokinetic Analysis

The pharmacokinetics analysis population consists of all patients who provide reportable plasma concentration and PK parameter data, and who have no significant protocol deviations or AEs that may impact on the PK.

10.7.1 AZD2014

AZD2014 plasma concentrations and all other relevant associated data (e.g sampling and dosing time information) taken following the first AZD2014 dose and following multiple dosing will be merged with similar data from other studies in order to estimate appropriate AZD2014 PK parameters for each patient using non-linear mixed effects population modelling techniques. PK analysis may be reported separately for each of the AZD2014 schedules.

PK parameters where possible will include plasma drug clearance (CL/F), estimated maximum drug concentration (Cmax), elimination half-life (t1/2) and volume of distribution (Vss/F). A covariate model (using demography parameters) will be added to the defined PK model. Modelling of the PK with pharmacodynamic endpoints, QTc, AEs and efficacy endpoints can then be undertaken as appropriate.

The results of any such analyses will be reported separately to the CSR for this study.

10.7.2 Fulvestrant

Where possible the PK parameter Css,min will be determined for fulvestrant in each treatment arm from the pre-dose plasma samples taken just before the fulvestrant injections on Cycle 2 Day 1 and Cycle 3 Day 1.

These values will be compared to reported trough concentrations from patients receiving fulvestrant 500mg as a single agent in other studies. The results of any such analyses will be reported separately to the CSR for this study.

The PK analysis will be reported separately to the CSR.

10.8 Exploratory Analysis

Exploratory analyses will include multivariate adjustments to assess PFS using the Cox model, and for the impact of several baseline factors and exploratory biomarkers (including activation of the PI3K pathway) on the estimates of treatment effect for PFS and survival.

Additional exploratory analyses will focus on change in tumour size at 16 weeks. The week 16 change in tumour size will also be presented graphically by waterfall plots for each treatment group which present each patient's Week 16 change in tumour size as a separate bar, with the bars ordered from the largest increase to the largest decrease. This plot will be repeated separately by treatment group for those patients whose tumour was PI3K-pathways activation-positive at entry, and also for the overall analysis but flagging (by colour or pattern) whether patients have aberrant PI3K-pathway activation or not. Reference lines at the +20% and -30% change in tumour levels will be added to the plots, which correspond to the changes in sum of TLs that would result in the TL responses of progression and partial response, respectively. In these waterfall plots (and also in the listings) the patients whose Week 16 change in tumour size is based on an imputation due to missing TL data but known to be progressors will be clearly identified (by different coloured bars for the waterfall plots and a flag in the listings). Frequencies of NTL progressions and new lesions at Week 16 will be presented together with the change in tumour size results in order to put the change in tumour size results into perspective.

10.9 Procedures for handling missing, unused, and spurious data

All available efficacy and safety data will be included in data listings and tabulations. No imputation of values for missing data will be performed. Patients who are treated with the study drug but have no documentation for safety will not be included in safety analyses, because their inclusion would only serve to dilute percentages of patients with adverse events or laboratory toxicities. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures.

10.10 Determination of sample size

The primary endpoint is PFS. The study has 99.9% power at the 5% 1-sided level of statistical significance to detect a hazard ratio of 0.4 (i.e. 150% improvement in median PFS from a control median of 3.7 months) by adding AZD2014 to fulvestrant. This analysis requires 57+73=130 PFS events from recruiting patients over 18 months with 18 months subsequent follow-up (using software package PASS) for each of the two dosing schedule. However, for 90% power, only 48 events are needed. The trial has also 80% power to detect a hazard ratio of 0.67 (i.e. 50% improvement in median PFS from a control median of 7.4 months by combining fulvestrant with AZD2014 relative to fulvestrant plus everolimus at the 10% 1-sided level of statistical significance (or equivalently with 90% power at the 20% level of statistical significance). This analysis requires 68+52=120 PFS events from patients recruited over 18 months with 18 months subsequent follow-up.

The trial is designed to obtain meaningful estimates of the hazard ratio for AZD2014 in all treated patients and in patients with PIK3CA-mutant tumours only. Assuming an incidence of PIK3CA mutations of approximately 40%,

the study has approximately 92% power at the 5% 1-sided level of statistical significance to detect a hazard ratio of 0.4 (i.e. 150% improvement in median PFS by adding the AZD2014 to fulvestrant). This analysis requires 52 PFS events from patients recruited over 18 months with 18 months subsequent follow-up. This subgroup analysis will have only 54% power with 48 events at the 10% level of significance to detect a hazard ratio of 0.67 by combining fulvestrant with AZD2014 relative to fulvestrant plus everolimus.

Allowing for potential annual loss to follow-up of up to 7% in each arm and imprecision in the estimated event rate the number of patients likely to be needed is approximately 300 with 90 patients in each of the two AZD2014 + Fulvestrant arms, 60 patients in the Everolimus + Fulvestrant arm and 60 patients in the Fulvestrant alone arm to ensure required number of events needed. The planned 18-months recruitment period for the 4-arm part of the study. The number of patients recruited to the 3-arm part of the study are additional to these 300 patients

10.11 Interim analysis

There is no formal interim analysis/stopping rule but an interim analysis is planned to provide an early trigger for additional development work of AZD2014. It is intended that this analysis will not impact the MANTA study in anyway and for this reason the outcome of this interim analysis will be kept confidential with an independent group providing only the response of 'GO' or 'WAIT' to the AZD2014 development team. . The analysis will be carried out when approximately 40% of the number of events required for the final analysis have occurred in each of the fulvestrant combined with AZD2014 vs fulvestrant alone comparisons:

- 52 events of PD per investigator assessment will have occurred in each of the fulvestrant combined with AZD2014 vs fulvestrant alone comparisons;

The study database will not be formally locked for the interim analysis; however efforts will be made to ensure that the data is as complete and clean as possible.

The interim analysis will be carried out on PFS, the primary outcome of the study, and the observed hazard ratios will be assessed by the independent group against predetermined cut-offs to provide the result of 'GO' or 'WAIT'. The cut offs will be calculated based on predictive power at least 6 months prior to the expected time of the interim analysis and provided to the independent group.

If a 'GO' cut-off is met for either of the fulvestrant combined with AZD2014 vs fulvestrant alone comparisons, a more detailed analysis of the study data (on the same database version) may be performed by an independent group (that may include members of the IDMC and/or third parties). The results of the more detailed interim analysis will be reviewed by the IDMC prior to release to a pre-defined group within AstraZeneca.

For the planned interim analysis the intention is not to calculate any p-values (the HRs will instead be compared against pre-defined cut-offs). However, if any p-values are calculated then an alpha spending function like the Haybittle–Peto boundary will be used.

If the result of the PFS interim analysis is 'WAIT' then no further analyses will be performed until the final analysis of the study.

11 ADMINISTRATIVE REQUIREMENTS

11.1 Good clinical practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drugs as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. A Trial Master file will be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

11.2 Ethical considerations

This trial will be conducted in compliance with the protocol, ICH - GCP, the Data Protection Act (DPA G0027154), the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004 no. 1031) and other regulatory requirements as appropriate. Ethics Committee (EC) approval will be obtained for this trial. The CECM or NCC will maintain contact with EC and submit any protocol amendments to them. The CECM or NCC will provide relevant documentation to participating centres. It will be the responsibility of the local investigator to obtain a Site Specific

Assessment (SSA) and other necessary local approval for the protocol, and to inform local committees of any subsequent amendments.

11.3 Regulatory status

The trial will be performed under Clinical Trial Authorisation (CTA). This is conditional on all reporting of adverse events being met, in particular Suspected Unexpected Serious Adverse Reactions (SUSARs). These must be reported promptly by centres to the trials centre who will forward them to the Competent Authority and EC (and other regulatory bodies if applicable), within the required timeframe. Reporting to non-UK competent authorities and ECs will be carried out by the respective NCC.

11.4 Trial Administration and Responsibilities

This trial is sponsored by Queen Mary Univeristy of London (QMUL). Sponsorship activities and delegated responsibilities are followed in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended and in line with the Research Governance Framework for Health and Social Care and the principles of GCP. QMUL agrees to allow inspection of their premises by the competent authorities. The following responsibilities have been delegated:

The Chief Investigator:

- Selection of investigators (delegated to the respective NCC for non-UK countries)
- Implementation of Urgent Safety Measures

To the Chief Investigator or a named deputy delegated in his absence:

- Prompt decision as to which serious adverse reactions are SUSARs; and
- Prompt reporting of that decision to CECM for onward reporting to the licensing authority.

To participating centres:

- Ensuring recording and prompt reporting of SAEs/SARs to the CECM
- Putting and keeping in place arrangements to adhere to the principles of GCP;
- Keeping a copy of all 'essential documents' (as defined under the principles of GCP) and ensuring appropriate archiving and destruction of documentation once the trial has ended as required by regulation 31 of the principal Regulations of the Medicines Human Use (Clinical Trials) Regulations 2004 implementing the commission directive 2005/28EC;
- Ensuring investigational medicinal products (IMPs) are made available to patients free of charge; and
- Taking appropriate urgent safety measures.

Responsibilities are defined in an agreement between an individual participating centre and the sponsor. Contracting of non-UK centres is delegated to the respective NCC. QMUL is responsible for administering funding and co-ordinating any required legal agreements and investigator statements. The delegation of sponsorship responsibilities does not impact on or alter standard NHS indemnity cover. The agreement of delegated responsibilities is viewed as a partnership and as such it is necessary to share pertinent information between QMUL and Chief Investigator, including proposed inspections by the Competent Authority and/or other regulatory bodies.

11.5 Trial Management Group

The TMG will consist of the chief investigator, members of the coordinating centre (Trial Coordinator, Project Manager, Senior Research Pharmacist and Statistician) and representatives from the National Coordinating Centres. PIs from selected sites may be invited to attend. The TMG will be responsible for overseeing day to day issues arising from the trial and for reporting to the TSC. The group will meet regularly, at least twice per year.

11.6 Trial Steering Group

The TSC will consist of two independent clinicians, including the chair, three principal investigators and a statistician who are responsible for reviewing the trial and provide ongoing independent, expert advice to the TMG.

The TSC will convene 6 months after the first patient has entered the study, which will assess the data primarily from the stand-point of safety and treatment deliverability. Further meetings are expected to be annual, but may be more frequent if requested by the TSC. The TSC will report back to the TMG.

11.7 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will consist of two independent clinicians and an independent statistician. The first safety review by the IDMC will take place after recruiting 20 patients. An additional safety review of the intermittent schedule is planned after 10 patients have been recruited to this treatment arm and dosed for at least 2 months. If this safety review demonstrates that >50% patients in the intermittent treatment arm require a dose reduction, the starting dose for patients subsequently enrolled to the intermittent arm will be reduced to 100mg BID 2/5 or the intermittent schedule will be discontinued. Patients recruited at 125mg BID will not be replaced.

The IDMC will subsequently review the trial on a 12 monthly basis to assess toxicity but may meet more frequently if requested by the IDMC. The conclusion will be fed back to the Trial Management Group.

The IDMC will also carry out an interim analysis to provide an early trigger for additional development work of AZD2014. The analysis will be carried out when approximately 40% of the number of events required for the final analysis have occurred in the specified comparisons. There is no formal stopping rule and the outcome of this analysis will be kept confidential with the IDMC providing only the response of 'GO' or 'WAIT' to the AZD2014 development team. .

If a 'GO' cut off is met, a more detailed analysis of the data may be performed by an independent group (that may include members of the IDMC and/or third parties). The results of the more detailed interim analysis will be reviewed by the IDMC prior to release to a pre-defined group within AstraZeneca. .

11.8 Informed consent

The sponsor's sample Patient Information Sheet and Informed Consent Form will be provided to each site. The sponsor or its designee must review and approve any proposed changes to the Sample Informed Consent Form or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before EC submission. Patients must be re-consented to the most current version of the Consent Forms only if signficant changes have been incorporated (i.e to process or patient commitments). The final EC-approved Consent Forms must be provided to the sponsor for regulatory purposes. The Informed Consent Form should be revised whenever there are changes to procedures outlined in the form or when new information becomes available that may affect the willingness of the patient to participate

The local investigator is required to explain the nature and purpose of the trial to the patient prior to trial entry. A detailed patient information sheet and consent form will be given to the patient and written informed consent obtained before trial entry. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s). The Consent Forms must be signed by the patient or the patient's legally authorised representative before her participation in the study. The case history for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorised representative. Where possible, it will be provided in a certified translation of the local language; if not possible an independent translator will be present at consenting process. All signed and dated Consent Forms must remain in each patient's study file and must be available for verification by study monitors at any time.

Patients entering the study where additional research biopsies are taken will be asked to sign the optional box on the consent form approved by a Research Ethics Committee for the tissue bank holding tissue pending entry to this study, provided a copy of the information and blank consent form have been approved by the Chief Investigator.

11.9 Data and Sample Acquisition

This trial uses electronic case report forms (eCRFs). Sites will receive training for appropriate CRF completion. CRFs will be submitted electronically to the sponsor and should be handled in accordance with the sponsor's instructions. Any data queries arising from initial review will be sent to the relevant centre for resolution.

All CRFs should be completed by designated, trained examining personnel or the study coordinator as appropriate. The CRF should be reviewed and electronically signed and dated by the investigator. In addition, at the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records.

The Trial Management Group reserves the right to amend or add to the CRFs as appropriate. Such changes do not constitute a protocol amendment, and revised or additional forms should be used by centres in accordance with the guidelines provided by the sponsor.

CECM will be responsible for monitoring transfer and receipt of biological specimens. Tracking forms will be sent by centres to CECM to monitor the transfer of all biological samples. All data will be handled, computerised and stored in accordance with the Data Protection Act 1998.

11.10 Study monitoring requirements

Site visits may be conducted by an authorised Sponsor representative to inspect study data, patient medical records, and CRFs. The Principal Investigator will permit Sponsor monitors/representatives and collaborators, ECs, and the respective national or local health authorities or to inspect facilities and records relevant to this study.

Study monitors will perform ongoing source data verification (SDV) to confirm that critical protocol data (i.e. source data) entered into the CRFs by authorised site personnel are accurate, complete, and verifiable from source documents.

Source documents are where patient data are recorded and documented for the first time. They include, but are not limited to, hospital records (paper and/or electronic), clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in a clinical trial.

Source documents that are required to verify the validity and completeness of data entered into the CRFs must never be obliterated or destroyed. To facilitate SDV, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and EC review. The investigational site must also allow inspection by applicable regulatory authorities.

11.11 On-site audits

Regulatory authorities and/or the EC may request access to all source documents, data capture records, informed consent forms, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

11.12 Data protection

The sponsor will comply with all aspects of the DPA 1998. Any requests from patients for access to data about them held at CECM should be directed to the Trial Coordinator in the first instance, who will refer the request to the Data Protection Officer at QMUL.

In order to maintain patient privacy, all data capture records, study drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. Each investigator should keep a separate log of all patients' Trial IDs, names, addresses and hospital numbers. The investigator must ensure the patients' confidentiality is maintained.

The investigator will grant auditor(s) from regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

11.13 Protocol compliance

The investigator will conduct the study in compliance with the protocol. Any approved modifications to the protocol will be informed to the participating sites by the Sponsor in writing. Any departures from the protocol must be notified to the Trials Office and fully documented in the source documentation and in deviation logs.

11.14 Premature closure of the study

This study may be prematurely terminated, if in the opinion of the TSC there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided. Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients

- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements

11.15 End of study

For the purposes of Clinical Trial Authorisation (CTA) under the European Union Directive 2001/20/EC, the study is deemed to have ended 30 days after the last patient receives the last dose of the investigational medicinal product (IMP). For all other purposes, the study end date is deemed to be the date of last data capture.

11.16 Record retention

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified according to ICH-GCP and applicable regulatory requirement(s). These documents should be classified into two different separate categories (1) Investigator's Study File, and (2) patient clinical source documents.

The Investigator's Study File will contain the protocol/amendments, Case Report and Query Forms, EC and governmental approval with correspondence, sample informed consent, drug records, delegation of responsibilities log, staff curriculum vitae and authorisation forms and other appropriate documents/correspondence.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs) would include patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, EEG, X-ray, pathology and special assessment reports, signed informed consent forms, consultant letters, and patient screening and enrolment logs. The investigator must keep these two categories of documents on file for **at least 20 years** after completion or discontinuation of the study, or later if this is policy of the local Trust. After that period of time the documents may be destroyed, according to local regulations.

If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. This needs to be documented in writing.

11.17 Indemnity

This study is an investigator-led trial designed by the Chief Investigator and the protocol development group. The study is sponsored by Queen Mary University of Lonodn (QMUL). Indemnity for participating hospitals is provided by the sponsor.

11.18 Publication of study findings and use of information

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. Data from all centres will be analysed together and published as soon as possible. Individual participants may not publish data concerning their patients that are directly relevant to questions posed by the trial until the Trial Management Group (TMG) has published its report. The TMG will form the basis of the Writing Committee and advice on the nature of publications. The main trial results will be published in the name of the trial in a peer-reviewed journal on behalf of all collaborators. Authorship of any secondary publications e.g. relating to the various biological studies will reflect the intellectual and time input into these studies, and might not be the same as on the primary publication. The information obtained from the clinical study will be used towards the development of study drug and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

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13 APPENDIX 1: PERFORMANCE STATUS (ECOG)

The following table presents the ECOG performance status scale:

GRADE	
0	Fully active and able to carry on all pre-disease performance without restriction. (Karnofsky 90-100).
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 (Karnofsky 70-80).
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 (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair (Karnofsky 10-20).

Table 14: ECOG performance status scale

14 APPENDIX 2: CONCOMITANT THERAPIES

14.1 Agents that should not be combined with AZD2014/everolimus

CYP3A5 and CYP3A4 were identified *in vitro* as the principal P450s responsible for human metabolism of AZD2014, indicating the possibility of drug-drug interactions with inhibitors and inducers of these enzymes. Co-administration of CYP3A4 or CYP3A5 inhibitors may increase exposure to AZD2014 and hence potentially affect efficacy/toxicity and hence increase the risk of time dependent inhibition (and resultant toxicity of CYP3A4 substrates). In addition, co-administration of CYP3A4 or CYP3A5 inducers may decrease the exposure to AZD2014 and hence potentially affect efficacy. AZD2014 showed no time dependent inhibition of CYPs, and only weak reversible inhibition of CYPs 2C8 (IC50 ≈ 21 μM). The possibility that AZD2014 may precipitate drug interactions due to inhibition of the drug metabolizing enzymes CYP2C8, CYP2C9, CYP2C19, CYP2D6, or the drug transporters Pgp (MDR1), BCRP, OATP1B1, OATP1B3, OCT1 and OCT2 cannot be excluded. Co-administration of AZD2014, particularly at high doses, with known or possible substrates of these enzymes / transporters may lead to their increased exposure and requires careful evaluation.

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of P-Glykoprotein (PgP). Therefore, absorption and subsequent elimination of everolimus may be influenced by products that affect CYP3A4 and/or PgP. *In vitro*, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6. Substances that are inhibitors of CYP3A4 or PgP may therefore increase everolimus blood concentrations by decreasing metabolism or the efflux of everolimus from intestinal cells. Substances that are inducers of CYP3A4 or PgP may decrease everolimus blood concentrations by increasing metabolism or the efflux of everolimus from intestinal cells.

The following restrictions will therefore be put in place in the study:

- Patients should avoid exposure to potent or moderate inhibitors or inducers of CYP3A4/5 within the following wash-out periods prior to the first dose of study treatment until 2 weeks after the last dose of study treatment.
    - Inhibitors (competitive): ketoconazole, itraconazole, posaconazole, indinavir, darunavir, nelfinavir, atazanavir, amprenavir, fosamprenavir, fluconazole, nefazodone, cimetidine, aprepitant, miconazole, fluvoxamine, conivaptan, cyclosporine, imatinib, netupitant, ciprofloxacin, dronedarone P-glycoprotein, grapefruit juice, or seville oranges (1 week minimum wash-out period), saquinovir, telithromycin, troleandomycin, voriconazole or idelalisib (2 week minimum wash-out period) amiodarone (27 week minimum wash-out period)
    - Inhibitors (time dependent): erythromycin, clarithromycin, verapamil, ritonavir, diltiazem, , bocepravir, cobicistat, danoprevir, elvitegravir, LCL161, lopinavir, mibefradil, posaconazole, telaprevir or tipranivir, ACT-178882, casopitant, crizotinib, darunavir, diltiazem, ledipasvir, lomitapide or tofisopam (2 week minimum wash-out period)
    - Inducers: bosentan, genistein, lersivirine, lopinavir, modafinil, nafcillin, ritonavir, semagacestat, thioridazine, tipranavir (1 week minimum wash-out period), etravirine (2 week minimum wash-out period), phenytoin, rifampicin, St. John's Wort, carbamazepine, dexamethasone, primidone, griseofulvin, carbamazepine, barbiturates, troglitazone, pioglitazone, oxcarbazepine, nevirapine, efavirenz, rifabutin, efavirenz (3 week minimum wash-out period) enzalutimide or phenobarbital (5 week minimum wash-out period), mitotane (114 weeks minimum wash-out period)
- Patients should avoid exposure to sensitive or narrow therapeutic range substrates of the drug metabolising enzymes CYP2C8, CYP2C9, CYP2C19, CYP2D6 or the drug transporters Pgp (MDR1), BCRP, OATP1B1, OATP1B3, OCT1 and OCT2 within the appropriate wash-out period before the first dose of study treatment until 2 weeks after the last dose of treatment. Examples of such substrates are provided in Tables 15 and 16 below.

Short term administration of moderate or potent CYP3A4/5 inhibitors or inducers may be permitted, although concomitant use could lead to lower plasma levels of AZD2014 and everolimus and a potential reduction in clinical efficacy. If co-administration is necessary then additional monitoring for signs of toxicity related to increased exposure to the substrates is required. Short term administration of known or possible substrates of CYP2C8, CYP2C9, CYP2C19, CYP2D6, Pgp (MDR1), BCRP, OATP1B1, OATP1B3, OCT1 and OCT2 enzymes / transporters may be permitted but for known or potential sensitive or narrow therapeutic range substrates the study drug should be withheld 3 days prior to the first dose and not restarted until at least the concomitant therapy has

been discontinued and the appropriate washout period elapsed. An increased frequency of monitoring of anticoagulation during treatment with AZD2014/everolimus is advised in patients who receive regular anticoagulant therapy; such patients should stop medication with AZD2014/everolimus if they experience CTCAE grade 3 thrombocytopenia.

CYP Enzymes	**Sensitive substrates**
CYP2C8	**Paclitaxel,** Repaglinide
CYP2C9	Celecoxib, **phenytoin, Warfarin**
CYP2C19	Diazepam, gliclazide, R-mephobarbital, pantoprazole, rabeprazole, tilidine, Lansoprazole, omeprazole, **S-mephenytoin**
CYP2D6	Codeine, doxepin, E-trans-doxepin, eliglustat, encainide, enclomiphene, fluoxetine, methoxyphenamine, nefazodone, nicergoline, paroxetine, perhexilline, prajmaline, propafenone, repinotan, risperidone, traxopridil, trimipramine, tropisetron, vernakalant, Atomoxetine, desipramine,dextromethorphan, metoprolol, nebivolol, perphenazine, **Thioridazine,** tolterodine, venlafaxine

Table 15: Examples of Sensitive In Vivo CYP Substrates of CYPs 2C8, 2C9, 2C19 & 2D6

Substrates in bold type have a narrow therapeutic index

Transporter	**Substrate**
P-gp	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan
BCRP	Methotrexate, mitoxantrone, imatinib, irrinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan, atorvastatin, fluvastatin, simvastatin
OATP	Atorvastatin, bosentan, fexofenadine, glybutride, pitavastatin, pravastatin, **repaglinide,** rosuvastatin, simvastatin
OCT	Certirizine, dofetilide, gabapentin, metformin, **pilsicainide**, pindolol, **procainamide,** ranitidine, varenicline

Table 16: Examples of In Vivo Substrates for Pgp, BCRP, OATP1B1, OATP1B3, OCT1 and OCT2 Drug Transporters

Substrates in bold type have a narrow therapeutic index

15 APPENDIX 3: GUIDELINES FOR EVALUATION OF OBJECTIVE TUMOUR RESPONSE USING RECIST CRITERIA (RESPONSE EVALUATION CRITERIA IN SOLID TUMOURS)

15.1 Introduction

This appendix details the implementation of RECIST 1.1 Guidelines (Eisenhauer et al 2009) with regards to Investigator assessment of tumour burden including protocol-specific requirements for this study.

15.2 Definition of measurable, non-measurable, target and non-target lesions

15.2.1 Measurable

A lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have a short axis ≥15 mm) with CT or MRI and which is suitable for accurate repeated measurements.

15.2.2 Non-measurable

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis at baseline*).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Previously irradiated lesions [9].
- Skin lesions assessed by clinical examination [10]
- Brain metastasis [2]

15.2.3 Special Cases

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.
- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient these should be selected as target lesions.

15.2.4 Target lesions

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as target lesions (TL) at baseline.

15.2.5 Non-Target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

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[9] Localised post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and must be selected as Non-Target Lesions (NTL) at baseline and followed up as part of the NTL assessment.

[10] Skin lesions assessed by clinical examination and brain lesions are considered as NTL.

15.3 Methods of assessment

The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits. A summary of the methods to be used for RECIST assessment is provided below and those excluded from tumour assessments for this study are highlighted, with the rationale.

Target Lesions	Non-Target Lesions	New Lesions
CT (preferred) MRI	CT (preferred) MRI Clinical examination X-ray, Chest x-ray	CT (preferred) MRI Clinical examination X-ray, Chest x-ray Ultrasound Bone Scan FDG-PET

Table 17: Summary of Methods of Assessment

15.3.1 CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

In the MANTA study it is recommended that CT examinations of the chest and abdomen will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous (i.v.) contrast media administration is the preferred method.

MRI should be used where CT is not feasible or it is medically contra-indicated. For brain lesion assessment, MRI is the preferred method.

15.3.2 Clinical examination

In the MANTA study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as target lesions if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

15.3.3 X-ray

In the MANTA study, chest x-ray assessment will not be used for assessment of TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

In the MANTA study plain x-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

15.3.4 Ultrasound

In the MANTA study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

15.3.5 Endoscopy and laparoscopy

In the MANTA study, endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

15.3.6 Tumour markers

In the MANTA study tumour markers will not be used for tumour response assessments as per RECIST 1.1.

15.3.7 Cytology and histology

In the MANTA study histology will not be used as part of the tumour response assessment as per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between response / stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or appearance of clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL, or disease progression due to new lesions.

15.3.8 Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI or Xray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

In the MANTA study isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and xray is recommended where bone scan findings are equivocal.

15.3.9 FDG-PET scan

In the MANTA study FDG-PET scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake* not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

* A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

15.4 Tumour response evaluation

15.4.1 Schedule of evaluation

Tumour assessments will be performed at screening (within 28 days prior to Day 1 of Cycle 1), every 8 weeks (±7 days) during the first 40 weeks, every 12 weeks (±7 days) thereafter, and when clinically indicated for all patients, including those with bone-only disease. This schedule is to be maintained and will not be shifted for treatment delays. If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression then the patient should still continue to be followed until objective disease progression as defined by RECIST 1.1.

Screening assessments will be performed using contrast-enhanced CT scans of the chest, abdomen and pelvis, with additional anatomy as clinically indicated by extent of disease[11]. Subsequent tumour assessments should include CT scans of the chest and abdomen and other sites of disease. MRI scans may be substituted for CT scans but MRI of the chest may only be performed with approval from the Sponsor. Additional anatomy may be imaged at follow-up on suspicion of new lesions.

Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of

[11] Patients who cannot tolerate CT with contrast, despite pre-medications, may undergo a non-contrast CT scan of the chest and MRI of the abdomen.

individual patients. Baseline assessments should be performed no more than 28 days before the start of study treatment, and ideally should be performed as close as possible to the start of study treatment. The same radiographic procedure used to define measurable disease sites at screening must be used throughout the study (e.g., the same contrast protocol for CT scans).

Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

An initial bone scan should be performed within 6 weeks prior to Day 1. For patients without known or suspected bone metastasis, follow-up bone scans are not required. Bone scans should only be repeated in the event of clinical suspicion of progression of existing bone lesions that cannot be visualised on CT or MRI, the development of new bone lesions or in the assessment of a CR, if any disease was evident at screening.

For patients with ***bone-only disease not visible on the CT or MRI scans*** being performed as part of the tumour assessments, bone scans should be repeated every 12 weeks (+/-7 days for flexibility in the event of isotope shortage), and when clinically indicated.

A documented standard-of-care tumour assessment performed within 28 days before Day 1 of Cycle 1 may be used for the screening assessment provided it meets the above requirements. The same imaging method used at screening must be used throughout the study. Response assessments will be performed by the investigator, on the basis of physical examinations and imaging scans, through use of RECIST v1.1.

15.4.2 Target lesions (TL)

Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TL at baseline.

Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), 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.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts.
- If two or more TL merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention e.g. radiotherapy, embolisation, surgery etc., during the study, the size of the TL should still be provided where possible.

Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumour visit response for TL

Best Response	Criteria for target lesion response
Complete Response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters (SD) of TL determined by 2 observations not less than 4 weeks apart and taking as reference the baseline sum SD. (the scheduled tumour evaluation is 9 weeks apart) It is not necessary for all lesions to have regressed to qualify for partial response, but no lesions must have progressed and not one additional new lesion should appear.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD determined by 2 observations not less than 4 weeks apart.
Progression (PD)	At least a 20% increase in the SD of target lesions taking as reference the smallest SD recorded since the treatment started or the appearance of one or more new lesions. Assignment to the progression category is done after 6 weeks from study entry. When the progression is observed before 6 weeks after entry in the study, the patient will be considered as an “early progression”.
Not Evaluable (NE)	Only relevant if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response

Table 18: Evaluation of Target-Measurable Lesions

15.4.3 Non-Target lesions (NTL)

Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

Best Response	Criteria for non-target lesion response
Complete Response (CR)	Disappearance of all NTLs determined by 2 observations not less than 4 weeks apart. All lymphnodes must be non-pathological in size (< 10 mm short axis).
Incomplete Response/ Stable Disease (SD)	Persistence of one or more NTLs
Progression (PD)	Appearance of one or more new lesions. Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy. NB: In the case of radiological evidence of progression in bone at cycle 2, the tumour flare phenomenon should be considered and excluded prior to assigning progression "PD" to the patient's disease.
Not Evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall non-target lesion assessment at this visit. Note: For patients without target lesions at baseline, this is relevant if any of the non-target lesions were not assessed at this visit and the progression criteria have not been met

Table 19: Evaluation of Non Target Lesions

To achieve 'unequivocal progression' on the basis of non-target lesions, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target lesions, 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

15.4.4 New lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

15.4.5 Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

15.4.6 Evaluation of Overall Visit Response

The overall visit response will be derived using the algorithm shown in Table 20.

Target Lesions	Non Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Incomplete Response / SD	No	PR
CR	NE	No	PR
PR	Non-PD	No	PR
SD	Non-PD or NE	No	SD
NA	Incomplete Response / SD	No	SD
NE	Non-PD or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 20: Determination of the overall response

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not applicable (only relevant if there were no TL/NTLs at baseline).

15.5 Specifications for radiological imaging

These notes are recommendations for use in clinical studies. The use of standardized protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

15.5.1 CT Scan

CT scans of the chest and abdomen should be contiguous throughout all the anatomic region of interest. The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

a. Anatomic coverage: Optimal anatomic coverage for most solid tumours is chest and abdomen. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

b. IV contrast administration: Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow- up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomi location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions,

since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study then the recommended methods are: CT thoracic examination without contrast and abdominal MRI with contrast. If MRI cannot be performed then CT without i.v. contrast is an option for the thorax and abdomen examination. For brain lesions assessment, MRI is the preferred method.

c. Slice thickness and reconstruction interval: It is recommended that CT scans be performed at 5mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not “selected” images of the apparent lesion.

15.5.2 MRI Scan

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the specific body part being imaged as well as the scanner utilised. It is beyond the scope appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible. For these reasons, CT is the imaging modality of choice.

Statistical Analysis Plan

TRIAL FULL TITLE	**A randomized Phase II study of Fulvestrant in combination with the dual mTOR inhibitor AZD2014 or Everolimus or Fulvestrant alone in Estrogen receptor-positive advanced or metastatic breast cancer**		
EUDRACT NUMBER	**2013-002403-34**		
SAP VERSION	**2.0**		
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TRIAL STATISTICIAN	**Dr. Shah-Jalal Sarker**		
Signature		*Date*	**2nd October 2017**
TRIAL CHIEF INVESTIGATOR	**Professor Peter Schmid**		
Signature		*Date*	**2nd October 2017**

Document History

Version	Date	Changes Made
1.0	16 April 2016	First version.
2.0	2nd October 2017	Second version – additional data cuts, and updates to endpoint definitions and calculations.

Table of Contents

Abbreviations and Definitions

Abbreviations	Definitions
AAS	AntiA sub-scale
AE	Adverse event
AI	Aromatase Inhibitor
AZ	AstraZeneca
CB	Clinical benefit
CBR	Clinical benefit rate
CECM	Centre for experimental cancer medicine
CI	Confidence interval
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for AEs
DNA	Deoxyribonucleic acid
ECOG	Eastern cooperative oncology group
ER	Estrogen receptor
ESS-23	Endocrine symptom sub-scale
FACTAnti-A-ES	Functional assessment of cancer therapy-breast-Anti-A and Endocrine Symptom
FACT-G	Functional assessment of cancer therapy-general
FWB	Functional well-being
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
IDMC	Independent data monitoring committee
IHC	Immunohistochemistry
IMP	Investigational medicinal product
IRF	Independent review facility
ITT	Intention-to-treat
IWRS	Interactive web response system
K-M	Kaplan-Meier
MEDRA	Medical dictionary for regulatory activities
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
mTORC1	mTOR complex 1
mTORC2	mTOR complex 2
NA	Not applicable
NCI	National cancer institute
NE	Not evaluable
NTL	Non-target lesions
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PI3K	Phosphoinositide 3-kinase
PID	Percentage intended dose
PK	Pharmacokinetic
PP	Per-protocol
PR	Partial response
PRO	Patient reported outcomes
PWB	Physical well-being
QMUL	Queen Mary University of London
QoL	Quality of life

QTcF	QTc calculated by Fridericia's formulae
RDI	Relative dose intensity
RECIST	Response evaluation criteria in solid tumours
RNA	Ribonucleic acids
SAE	Serious adverse event
SD	Stable disease
SS	Safety set
TL	Target lesion
TMF	Trial master file
TOI	Trial outcome index

1 Introduction

1.1 Preface

Resistance to endocrine therapy remains a major clinical challenge in Estrogen receptor (ER) positive (ER+ve) breast cancer. Aberrant Phosphoinositide 3-kinase (PI3K)/AKT/mammalian Target of Rapamycin (mTOR) pathway activation frequently occurs in ER+ve breast cancer and has been associated with resistance to endocrine therapy. Randomised clinical trials have demonstrated a substantial benefit of adding Everolimus to endocrine treatment. However, there is increasing evidence that inhibition of only mTOR complex 1 (mTORC1) with rapalogues such as Everolimus sets off a negative feedback mechanism that leads to increased AKT signalling and is linked with treatment resistance. AZD2014 is a dual inhibitor of both mTORC1 (rapamycin-sensitive) and mTOR complex 2 (mTORC2) (rapamycin insensitive); compared to rapalogues, AZD2014 has a broader range of growth inhibitory activity in preclinical models based on a more profound mTORC1 inhibition and the additional inhibition of mTORC2. AZD2014 is especially effective in ER+ve breast cancer models, showing superior activity to Everolimus both in hormone-sensitive and resistant models.

1.2 Purpose of the Analyses

Study analyses will assess the efficacy and safety of AZD2014 in combination with Fulvestrant, the pharmacokinetics (PKs) of this combination as well as the impact on the patient's quality of life (QoL) and will be included in the clinical study report (CSR). An interim efficacy analysis will be carried out to provide an early trigger for additional development work of AZD2014. The interim analysis will not impact on the conduct of MANTA in any way.

2 Study Objectives and Endpoints

Primary Objective	**Endpoints**
Estimate the clinical benefit of Fulvestrant + AZD2014 (continuous daily schedule) relative to Fulvestrant alone, as measured by investigator-assessed progression-free survival (PFS).	PFS, defined as the time from the date of randomisation to the date of first documented tumour progression based on investigator assessment (using Response evaluation criteria in solid tumours [RECIST] v1.1) or death from any cause, whichever occurs first.
Secondary Objectives	**Endpoints**
Estimate the clinical benefit of Fulvestrant + AZD2014 (continuous daily schedule) relative to Fulvestrant + Everolimus, as measured by investigator-assessed PFS.	As per the primary objective endpoint.
Estimate the clinical benefit of Fulvestrant + AZD2014 (intermittent schedule) relative to Fulvestrant + Everolimus or Fulvestrant alone, as measured by investigator-assessed PFS.	As per the primary objective endpoint.
Estimate the clinical benefit of Fulvestrant + AZD2014 (continuous daily schedule) relative to Fulvestrant + AZD2014 (intermittent schedule), as measured by investigator-assessed PFS.	As per the primary objective endpoint.
Assess the clinical activity, as measured by objective response rate (ORR) (RECIST v1.1), clinical benefit rate (CBR), duration of clinical	Objective response, defined as a complete (CR) or partial response (PR), based on investigator assessment (using RECIST v1.1).

benefit (CB) and duration of response, of Fulvestrant + AZD2014 relative to Fulvestrant + Everolimus or Fulvestrant alone.	CB, defined as number of patients with CR or PR or stable disease (SD) maintained ≥24 weeks from the date of randomisation, based on investigator assessment using RECIST v1.1.
	Duration of CB, defined as the time from randomisation to disease progression based on investigator assessment using RECIST v1.1, or death from any cause, whichever occurs first in patients with CB.
	Duration of response, defined as the time from randomisation to disease progression based on investigator assessment using RECIST v1.1, or death from any cause, whichever occurs first in patients with objective response.
Estimate the overall survival (OS) benefit of Fulvestrant + AZD2014 relative to Fulvestrant + Everolimus or Fulvestrant alone.	OS, defined as the time from date of randomisation to the date of death due to any cause.
Investigate the effects of Fulvestrant +/- AZD2014 or Everolimus on bone-turnover biomarkers.	Percentage change in serum of serum beta C-terminal cross-linking telopeptide of Type I collagen (βCTx) and N-terminal propeptide of Type I procollagen (PINP) from screening/baseline to each time that samples are collected.
Compare the differences in patient reported outcomes (PROs) as measured by the Functional Assessment of Cancer Therapy-General (FACT-G) scale together with the Breast-Anti-A and Endocrine Symptom (FACTAnti-A-ES) subscales.	PROs, as assessed by FACT-G questionnaire together with the FACT-Anti-A, and FACT-ES Subscales. **Note**: Not all patients will contribute to this endpoint. Contribution will be dependent on the availability of the relevant questionnaire in the local language.
Investigate the PKs of AZD2014 in breast cancer patients co-administered with Fulvestrant.	Assess PK parameters of AZD2014 when co-administered with Fulvestrant to breast cancer patients.
Determine the minimum plasma concentration at steady state in breast cancer patients of Fulvestrant alone and when administered in combination with AZD2014 or Everolimus.	PK assessment of Fulvestrant when administered alone and in combination with AZD2014 or Everolimus to breast cancer patients.
Safety Objectives	**Endpoints**
Establish the safety and tolerability of: • Fulvestrant + AZD2014 relative to Fulvestrant + Everolimus or Fulvestrant alone.	Incidence of serious adverse events (SAEs).
	Incidence of grade 3 and 4 adverse events (AEs) (Common Terminology Criteria for AEs [CTCAE], version 4.0.3).
	Incidence of all AEs of all grades.
Establish the safety of: • The intermittent schedule of AZD2014 relative to the continuous daily schedule of AZD2014.	Incidence of the following selected AEs (any grade): • Hyperglycaemia • Diarrhoea • Stomatitis

	• Rash • Interstitial pneumonitis • Fatigue • T-Wave changes
	AEs leading to discontinuation of the study medication.
	Changes in vital signs and clinical laboratory results during and following study drug administration.
Exploratory Objectives	**Endpoints**
Estimate the clinical activity (as measured by ORR, duration of response, and CBR) of Fulvestrant + AZD2014 (continuous schedule) in patients who switch to this treatment after progression on Fulvestrant + Everolimus.	As per the secondary objectives endpoints of ORR, duration of response, and CBR.
Estimate the clinical benefit of Fulvestrant + AZD2014 relative to Fulvestrant + Everolimus or Fulvestrant alone: • in patients with and without aberrant activation of the PI3K/AKT/mTOR pathway • in patients with primary or secondary endocrine resistance	As per the primary objective endpoint of PFS based on investigator assessment (using RECIST v1.1).
Explore potential biomarkers that may help predict response to Fulvestrant + AZD2014 compared with Fulvestrant + Everolimus or Fulvestrant alone.	Alterations in deoxyribonucleic acid (DNA) and ribonucleic acids (RNA), including mutational status, RNA expression levels, DNA copy number, and protein expression.
Investigate the relationship between AZD2014 PK and clinical outcomes (e.g. efficacy and safety parameters).	The PK outcome measures for this study are as follows: • Plasma drug clearance (CL/F), estimated maximum drug concentration (C_{max}), elimination half-life ($t_{1/2}$) and volume of distribution (Vss/F) for AZD2014. • Css_{min} for Fulvestrant.

3 Study Methods

3.1 General Study Design and Plan

This is an international, open-label, multicentre, 4-arm randomised phase II trial of Fulvestrant + AZD2014 at a continuous daily schedule and Fulvestrant + AZD2014 at an intermittent schedule (2 days on, 5 days off) versus Fulvestrant + Everolimus versus Fulvestrant alone in patients with ER-positive, Human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer, whose disease relapsed during treatment with (or within 12 months after discontinuation of) an Aromatase Inhibitor (AI) in the adjuvant setting or progressed during treatment with an AI in the metastatic setting.

The original study was designed as a 3-arm phase II trial in the same patient population, randomising patients (1:2:1) to Fulvestrant, Fulvestrant + AZD2014 or Fulvestrant + Everolimus, but was amended to incorporate a 4th arm in which AZD2014 will be given at an intermittent schedule (2 days on, 5 days off). Patients recruited in the 3-arm design will be included in the analyses in this study.

Patients will be randomised (2:3:3:2) to one of the four treatment arms:

- Fulvestrant
- Fulvestrant + AZD2014 (continuous daily schedule)
- Fulvestrant + AZD2014 (intermittent schedule - 2 days on, 5 days off)
- Fulvestrant + Everolimus

Randomization will be stratified by the following criteria:

- Measurable disease (vs. non-measurable).
- Sensitivity to prior endocrine therapy (sensitive versus resistant)

Sensitivity to prior endocrine therapy is defined as (i) at least 24 months of endocrine therapy before recurrence in the adjuvant setting or (ii) a CR or PR to at least one line of prior metastatic endocrine treatment, or (iii) stabilization for at least 24 weeks of at least one line of endocrine therapy for locally advanced and/ or metastatic breast cancer.

Treatment will be continued until disease progression unless there is evidence of unacceptable toxicity, or if the patient requested to be withdrawn from the study. If one of the treatments (Fulvestrant or mTOR inhibitor) is discontinued prior to disease progression, patients should be continued on single agent treatment until progression or evidence of unacceptable toxicity.

At the time of documented disease progression (using RECIST v1.1), patients randomized to receive Fulvestrant + Everolimus who still meet eligibility criteria may be permitted to switch treatment with Fulvestrant + AZD2014 (continuous schedule). Treatment switch must begin no later than 28 days after the clinic visit at which progression is determined. Patients will receive switched treatment until progression, intolerable toxicity, elective withdrawal from the study, or until the completion or termination of the study, whichever occurs first.

Tumour evaluations will be performed before the initiation of treatment, every 8 weeks during the first 40 weeks and every 12 weeks thereafter until disease progression. The study will also assess the relationship between the anticipated anti-tumour activity of the treatment regimen and biological characteristics of patients' tumour at baseline. This is summarised in Figure 1.

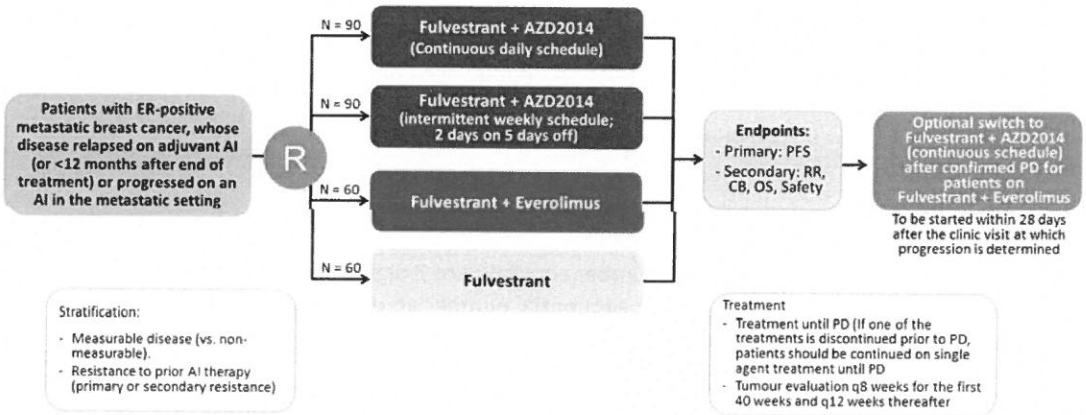


Figure 1: Overall study design

3.2 Inclusion-Exclusion Criteria and General Study Population

Post-menopausal women with ER+ve, HER2-ve advanced or metastatic, hormone refractory breast cancer, who have at least one measurable lesion (RECIST v1.1) or lytic/missed bone lesions in the absence of measurable disease and no life-threatening visceral disease will be included in this trial.

ER+ve is defined as ≥ 1% of tumour cells positive for ER on immunohistochemistry (IHC) or IHC score (Allred) ≥ 3 and HER2-ve is defined as 0, 1+ or 2+ on IHC and no evidence of amplification on ISH. Patients with significant pulmonary dysfunction, cardiovascular disease or uncontrolled diabetes are excluded. Patients must not have been previously treated with Fulvestrant, PI3K/Akt or mTOR inhibitors and must have had no more than one line of prior chemotherapy for metastatic breast cancer. Full inclusion and exclusion criteria can be found in Section 5 of the protocol.

3.3 Randomisation and Blinding

Once it has been confirmed that a patient meets all inclusion and exclusion criteria, they will be randomised to receive Fulvestrant, Fulvestrant + AZD2014 at a continuous daily schedule, Fulvestrant + AZD2014 at an intermittent schedule (2 days on, 5 days off), or Fulvestrant + Everolimus in a 2:3:3:2 ratio. Randomisation will be stratified by the following two factors:

- measurable disease (measurable vs. non-measurable), and
- sensitivity to prior endocrine therapy (sensitive versus resistant).

Measurable disease is defined as having at least one measurable lesion, not previously irradiated, which is ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

Sensitivity to prior endocrine therapy is defined as (i) at least 24 months of endocrine therapy before recurrence in the adjuvant setting or (ii) a CR or PR to at least one line of prior metastatic endocrine treatment, or (iii) stabilization for at least 24 weeks of at least one line of endocrine therapy for locally advanced and/ or metastatic breast cancer.

Randomisation is carried out directly by sites via the Cenduit Interactive Web Response System (IWRS) (Internet Interface). Randomisation will be restarted following the switch from the three-arm to the four-arm version of the study. There is a possibility of a short break in recruitment during this period. Sites will be given access to IWRS. Study staff at sites will then receive the result of the randomisation along with the patient trial number via email generated by IWRS.

Randomisation codes are not included in the SAP but will be included in the final CSR. The randomisation code is stored with Fisher Clinical Services and Cenduit. Randomisation codes can be obtained by contacting the MANTA Fisher Clinical Supplies contact. Full contact details can be found in the most up to date version of the MANTA Cenduit communication plan.

Patient trial IDs are as described in the table below:

Data Identifiers	Format	Example
Site Number	2 digits, with leading zero allowed (00-99)	12
Screening number	4 digits - SXXX	S001
Patient Number	5 digit number consisting of 2 digit site number followed by 3 digit sequential number across study starting at 001	12002
Randomisation Number	Same as patient number	12002
Shipment number	Seven digits starting at 1000000	1000123
Patient initial	3 characters, alphanumeric, site entered, hyphen acceptable as middle character	K-T

Patients should receive their first dose of study treatment no later than 14 days after randomisation.

3.4 Study Variables

3.4.1 Primary and Secondary Variables

3.4.1.1 Derivation of RECIST Visit Responses

For all subjects, the RECIST tumour response data will be used to determine each subject's visit response according to RECIST v1.1. It will also be used to determine PFS, ORR, CBR, duration of response and duration of CB.

Tumour assessments: Screening assessments will be performed using contrast-enhanced CT scans of the chest, abdomen and pelvis, with additional anatomy as clinically indicated by extent of disease. Patients who cannot tolerate CT with contrast, despite pre-medications, may undergo a non-contrast CT scan of the chest and MRI of the abdomen. Subsequent tumour assessments should include CT scans of the chest and abdomen and other sites of disease. MRI scans may be substituted for CT scans but MRI of the chest may only be performed with approval from the Sponsor. If a change in method of assessment occurs between CT and MRI this will be considered acceptable and no adjustment is needed. Additional anatomy may be imaged at follow-up on suspicion of new lesions.

Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Baseline assessments should be performed no more than 28 days before the start of study treatment, and ideally should be performed as close as possible to the start of study treatment. The same radiographic procedure used to define measurable disease sites at screening must be used throughout the study (e.g., the same contrast protocol for CT scans).

Tumour assessments will be performed at screening (within 28 days prior to Day 1 of Cycle 1), every 8 weeks (±7 days) during the first 40 weeks, every 12 weeks (±7 days) thereafter, and when clinically indicated for all patients, including those with bone-only disease. This schedule is to be maintained and will not be shifted for treatment delays. If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression then the patient should still continue to be followed until objective disease progression as defined by RECIST v1.1, death or withdrawal of consent, whichever occurs first.

Bone scans: An initial bone scan should be performed within 6 weeks prior to Day 1 of Cycle 1. For patients without known or suspected bone metastasis, follow-up bone scans are not required. Bone scans should only be repeated in the event of clinical suspicion of progression of existing bone lesions that cannot be visualised on CT or MRI, the development of new bone lesions or in the assessment of a CR, if any disease was evident at screening. For patients with bone-only disease not visible on the CT or MRI scans being performed as part of tumour assessments, a bone scan should be repeated every 12 weeks (+/-7 days) and when clinically indicated.

Additional scans: Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

Evaluation: Equivocal new lesions may be further evaluated by other modalities (biopsy, positron emission tomography, MRI, or CT scans, or plain radiographs). If the lesions remain equivocal, the investigator should use his or her judgment with regard to recording the finding as a new lesion on the Tumour Evaluation case report form (CRF). If a new lesion is recorded, the tumour response should

be recorded as progressive disease (PD). If the lesion remains equivocal and in the investigator's opinion is likely not reflective of PD, the lesion should not be recorded as a new lesion, and the patient may remain on study drug. This applies to new lesions identified by bone scan or any tumour assessment modality.

From the investigator's review of the imaging scans, the RECIST tumour response data will be used to determine each subject's visit response according to RECIST v1.1. If a subject has had a tumour assessment which cannot be evaluated then the subject will be assigned a visit response of not evaluable (NE) (unless there is evidence of progression in which case the response will be assigned as PD).

Target lesion (TL) progression will be calculated in comparison to when the tumour burden was at a minimum (i.e. smallest sum of diameters previously recorded on study). In the absence of objective progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

If the Investigator is in doubt as to whether objective progression has occurred, particularly with response to non-target lesions (NTLs) or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment and reassess the patient's status. Alternatively, repeat assessments might be scheduled earlier if clinically indicated. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of objective progression.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in 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 NTLs is usually not sufficient to quality for unequivocal progression status.

The primary PFS analysis for this study will be based on local review at participating centres. In addition, all radiographs including bone scans obtained as part of the protocol-required tumour assessments (including interval assessments obtained that documented progression of disease if applicable or for confirmation of objective response, if performed) will also be submitted to an independent review facility (IRF). A comparison will be made during the study to determine if there is a significant difference between the investigator and IRF assessments. If no difference exists, then no analyses will be performed based on IRF assessment. If there is a significant difference, the IRF assessment will be the basis for a secondary PFS analysis and also for secondary analysis of all other efficacy endpoints.

Radiological examinations performed in the conduct of this study for RECIST response assessments must be retained at site as source data and a copy anonymised for personal identifiers, e.g. name, initials, be available for collection by the Sponsor to support any future regulatory requests.

Documentation of target lesions (TLs)

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TLs at baseline. If more than one baseline scan is recorded then measurements from the one that is closest and prior to randomisation will be used to define the baseline sum of TLs.

TLs should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), 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.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimetres. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts.
- If two or more TL merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention e.g. radiotherapy, embolisation, surgery etc., during the study, the size of the TL should still be provided where possible.

Evaluation of target lesions (TLs)

This section provides the definitions of the criteria used to determine objective tumour visit response for TL:

Visit Reponses	Description
Complete Response (CR)	Disappearance of all target lesions (TLs). Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters as long as criteria for PD are not met.
Progressive disease (PD)	A ≥ 20% increase in the sum of diameters of TLs and an absolute increase of ≥ 5mm, taking as reference the smallest sum of diameters since treatment started including the baseline sum of diameters.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Not Evaluable (NE)	Only relevant in certain situations (i.e. if any of the TLs were not assessed or NE or had a lesion intervention at this visit; and scaling up could not be performed for lesions with interventions). Note: If the sum of diameters meets the PD criteria, PD overrides NE as a TL response.
Not applicable (NA)	No TLs are recorded at baseline.

Non-target lesions (NTL)

Evaluation of non-target lesions (NTLs)

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

Visit Responses	Description
Complete Response (CR)	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10 mm short axis).
Progressive Disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Non-CR/Non-PD	Persistence of one or more NTLs with no evidence of progression.
Not Evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
Not Applicable (NA)	Only relevant if there are no NTLs at baseline.

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR TLs, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

New lesions

Details of any new lesions will also be recorded with the date of assessment. New lesions will be identified via a Yes/No tick box. The absence and presence of new lesions at each visit should be listed alongside the TL and NTL visit responses. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

Evaluation of overall visit response

The overall visit response will be derived using the algorithm shown in the table below:

Target Lesions (TLs)	Non-Target Lesions (NTLs)	New Lesions	Overall Response
CR	CR or NA	No (or NE)	**CR**
CR	Non-CR/Non-PD or NE	No (or NE)	**PR**
PR	Non-PD or NE or NA	No (or NE)	**PR**
SD	Non-PD or NE or NA	No (or NE)	**SD**
PD	Any	Any	**PD**
Any	PD	Any	**PD**
Any	Any	Yes	**PD**
NE	Non-PD or NE or NA	No (or NE)	**NE**
NA	CR	No (or NE)	**CR**
NA	Non-CR/Non-PD	No (or NE)	**SD**
NA	NE	No (or NE)	**NE**

CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease, NE=not evaluable, NA=not applicable (only relevant if there were no TL/NTLs at baseline).

3.4.2 Outcome Variables

3.4.2.1 Primary Efficacy Variable

3.4.2.1.1 Progression-Free Survival (PFS)

PFS is defined as the time from the date of randomisation to the date of first documented tumour progression or death from any cause, whichever occurs first. For patients who have not died or experienced disease progression at the end of study, PFS will be censored on the last date the patient was known to be progression-free. The PFS time will always be derived based on scan/assessment dates not visit dates.

For patients with measurable disease at baseline, progression will be determined according to the RECIST criteria. **In the absence of measurable disease at baseline**, patients with bone only lesions, lytic or mixed (lytic + sclerotic), will be allowed to enter the study and the following will be considered disease progression among these patients:

- The appearance of one or more new lytic lesions in bone
- The appearance of one or more new lesions outside of bone
- Unequivocal progression of existing bone lesions

Note: Pathologic fracture, new compression fracture, or complications of bone metastases will not be considered as evidence of disease progression, unless one of the above-mentioned criteria is fulfilled.

3.4.2.2 Secondary Efficacy Variables

3.4.2.2.1 Objective Response

Objective response will be calculated in patients with measurable disease at baseline. Patients without measurable disease at baseline will not be included in this analysis. Patients without a post-baseline tumour assessment will be considered to be non-responders.

ORR is defined as number of patients with at least one visit response of CR or PR divided by the number of patients in the analysis.

For patients with an objective response, duration of response is defined as the time from randomisation to disease progression or death on study from any cause, whichever occurs first. Methods for handling censoring and for analysis are the same as those described for PFS.

Objective response analyses will be performed based on investigator assessment.

3.4.2.2.2 Clinical Benefit (CB)

CB will be calculated in patients with measurable disease at baseline. Patients without measurable disease at baseline will not be included in this analysis. Patients without a post-baseline tumour assessment will be considered to have no CB.

CBR is defined as number of patients with CR or PR or SD maintained ≥24 weeks from the date of randomisation divided by the number of patients in the analysis.

For patients with a CB, duration of CB is defined as the time from randomisation to disease progression or death on study from any cause, whichever occurs first. Methods for handling censoring and for analysis are the same as those described for PFS.

CB analyses will be performed based on investigator assessment.

3.4.2.2.3 Overall Survival (OS)

OS is defined as the time from date of randomisation to the date of death due to any cause. All deaths will be included, whether they occur on study treatment or following treatment discontinuation. For patients who have not died, OS will be censored at the date of last contact. Methods for handling censoring and for analysis are the same as those described for PFS.

3.4.2.3 Other Variables

3.4.2.3.1 Patient Reported Outcomes (PRO): Quality of Life (QoL) and Symptom Endpoints

Overall QoL will be measured using the FACT-G questionnaire together with 2 standardised and validated subscales the FACT-Anti-A, and FACT-ES. Participation of patients in these QoL assessments will depend on the availability of the questionnaires in the local language, as described in the following table:

Country	FACT-G	Anti-A-ES
UK	Yes	Yes
Germany	Yes	Yes
Spain	Yes	Yes
Portugal	Yes	Yes
Hungary	Yes	No
France	Yes	FACT-ES only, not Anti-A subscale
South Korea	Yes	FACT-ES only, not Anti-A subscale
Romania	Yes	No
Georgia	Yes	No

All these have been used to determine cancer and breast-cancer specific QoL and symptoms in numerous surgical and novel systemic therapy clinical trials assessing the efficacy and safety.

The questionnaires will be administered at baseline prior to randomisation and returned to the coordinating QoL centre. Thereafter patients should complete questionnaires prior to certain

scheduled visits with the physician during the study treatment period, and at the End of Treatment Visit.

The FACT-G scale is a 27 item, self-administered, multidimensional, validated and reliable patient questionnaire that evaluates and quantifies cancer QoL across several dimensions (physical, functional emotional and social well-being and well-being). Patients respond to each item on a 5-point Likert-type scale ranging from 0 (not at all) to 4 (very much). On average, it requires less than 10 minutes to complete the questionnaire. An overall HRQoL score can be calculated, with higher scores reflecting better HRQoL. The FACT-G total score ranges from 0 (impaired QoL) to 185 (unimpaired QoL).

The Anti-A (FACT-Anti-A) subscale has 24 additional items and the FACT-ES 19 items. When all subscales are used in combination, four nausea, SOB, joint pain and diarrhoea are only asked to avoid overlap and double counting. Each subscale is an independently validated tools designed specifically for use with the FACT-G to assess the symptoms related to endocrine therapies (FACT-ES) and those of small molecule inhibitors (FACT-Anti-A). We will therefore cover most of the recognised main toxicities of Fulvestrant, Everolimus or AZD2014.

To reduce missing data, the FACT-G -Anti-A and ES assessment questionnaires will be administered by the centres before the patient sees the physician at baseline (screening), and thereafter sent by post by the coordinating centre for completion on Day 1 of every cycle for the first 4 cycles, at 24 weeks, every 12 weeks thereafter and at the End of Treatment Visit.

There are very clear imputation rules for calculation of FACT scores in the FACIT Handbook.

The primary endpoints will be two Trial Outcome Index (TOI) i.e. TOI-Anti-A and Toi-ES comprised of physical, functional, anti-A and endocrine symptom subscale scores. This is calculated as the sum of the Physical well-being (PWB), Functional well-being (FWB), AntiA sub-scale (AAS) domains of FACT-AntiA for the TOI-Anti-A and Endocrine Symptom sub-scale (ESS-23) domain of the FACT- ES for the TOI-ES. The TOI will be summarized over time using raw score or pro-rated scores of missing data and change from baseline and percent change from baseline.

The secondary endpoints will comprise the following:

- An overall HRQOL score from the total FACT-G-AA-ES scales will be computed as the sum of the FACT-G and the specific AA and ES domains i.e. sum of 6 subscales (PWB, SWB, EWB, FWB, AAS, ESS-23).
- Individual subscale scores from the 6 subscales (PWB, SWB, EWB, FWB, AAS, ESS-23).

These scores will be summarized over time using raw score or pro-rated (see text below) scores of missing data and change from baseline and percent change from baseline.

Further details on PROs are given in the below documents:


doc01_Administrati on%20Guidelines_M


doc03_ScoringFACT -G%20v4-REVISED.p


manual.pdf


ScoringFACT-AntiA. pdf


ScoringFACT-ES%20 v4-REVISED3-No%2C

For each domain (PWB, SWB, EWB, FWB, AAS, ESS-23) if more than 50% of the items were answered (e.g., a minimum of 4 of 7 items, 4 of 6 items, etc.), the domain score can be prorated within each domain. This is done by multiplying the sum of the domain scores by the number of items in the domain, then dividing by the number of items actually answered. This can be done by using the formula below:

Prorated subscale score = [Sum of item scores] x [N of items in domain] ÷ [N of items answered]

The total score for each variable (TOI and overall HRQoL) is calculated as the sum of the un-weighted prorated scores. However, if at least 50% of the domain items are missing, that domain will be treated as missing and thus non-evaluable. If a domain score is non-evaluable, any HRQoL variable which these domains contribute to is also termed non-evaluable. For example, for the TOI variable if PWB is non-evaluable at a visit, the TOI variable is also non-evaluable at this visit. Furthermore, for the overall HRQoL variable if any domain score is non-evaluable then the overall HRQoL score is also non-evaluable at this visit.

4 Sample Size

The primary endpoint is PFS. The study has 99.9% power at the 5% 1-sided level of statistical significance to detect a hazard ratio (HR) of 0.4 (i.e. 150% improvement in median PFS from a control median of 3.7 months) by adding AZD2014 to Fulvestrant. This analysis requires 57+73=130 PFS events from recruiting patients over 18 months with 18 months subsequent follow-up (using software package PASS) for each of the two dosing schedule.

However, for 90% power, only 48 events are needed. The trial has also 80% power to detect a HR of 0.67 (i.e. 50% improvement in median PFS from a control median of 7.4 months by combining Fulvestrant with AZD2014 relative to Fulvestrant plus Everolimus at the 10% 1-sided level of statistical significance (or equivalently with 90% power at the 20% level of statistical significance). This analysis requires 68+52=120 PFS events from patients recruited over 18 months with 18 months subsequent follow-up.

The trial is designed to obtain meaningful estimates of the HR for AZD2014 in all treated patients and in patients with PIK3CA-mutant tumours only. Assuming an incidence of PIK3CA mutations of approximately 40%, the study has approximately 92% power at the 5% 1-sided level of statistical significance to detect a HR of 0.4 (i.e. 150% improvement in median PFS by adding the AZD2014 to Fulvestrant). This analysis requires 52 PFS events from patients recruited over 18 months with 18 months subsequent follow-up. This subgroup analysis will have only 54% power with 48 events at the 10% level of significance to detect a HR of 0.67 by combining Fulvestrant with AZD2014 relative to Fulvestrant plus Everolimus.

Allowing for potential annual loss to follow-up of up to 7% in each arm and imprecision in the estimated event rate the number of patients likely to be needed is approximately 300 with 90 patients in each of the two AZD2014 + Fulvestrant arms, 60 patients in the Everolimus + Fulvestrant arm and 60 patients in the Fulvestrant alone arm to ensure required number of events needed. The planned 18-months recruitment period for the 4-arm part of the study. The number of patients recruited to the 3-arm part of the study are additional to these 300 patients.

5 General Considerations

5.1 Timing of Analyses

MANTA opened to recruitment in January 2014 with the 3 arm design and in June 2014 the 4 arm design was implemented. The study is scheduled to complete recruitment in Q3/Q4 2016. 16 patients were recruited in the 3 arm design and the target for the 4 arm design is 300 patients. End of recruitment is deemed to have completed when a total of 316 patients have been recruited.
If recruitment is completed as per schedule then it is estimated that the following analyses will be carried out:

- An interim analysis will be carried out when approximately 40% of the number of events required for the final analysis have occurred in each of the Fulvestrant combined with AZD2014

vs Fulvestrant alone comparisons i.e. 52 events of PD per investigator assessment will have occurred in each of the Fulvestrant combined with AZD2014 vs Fulvestrant alone comparisons. The interim analysis is expected to take place in Q3 2016.

- Primary endpoint analysis is expected to be carried out in Q3 2017. A safety analysis may also be carried out at this stage.
- OS analysis will be carried out in Q4 2018, based on the assumption of a median OS of 24 months.
- Overall study analyses including QoL outcomes and translational endpoints are estimated to take place in Q4 2018.

5.2 Analysis Sets

5.2.1 Definition of Analysis Sets

5.2.1.1 Intention-To-Treat (ITT) Population

This population includes all patients randomised into the trial, regardless of whether they were later found to be ineligible, a protocol violator, or given the wrong treatment allocation. All efficacy analysis will be performed on an ITT basis, and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. Subjects who were randomised but did not subsequently go on to receive study treatment are not included in the ITT population. This may be considered as modified ITT population.

Efficacy endpoints will be analysed according to ITT analysis based on all patients (including the additional patients from the three-arm version of the trial). Sensitivity analysis will be carried out by separately analysing those patients in the four-arm part of the study.

5.2.1.2 Per-Protocol (PP) Population

The secondary efficacy analyses relating to ORR and CB will be performed on a PP basis, and will compare the treatment groups on the basis of treatment actually received.

5.2.1.3 Safety Set (SS) Population

This population includes all recruited patients who received at least one dose of study treatment with patients analysed according to the treatment they actually received. Randomised patients who did not receive any doses of study treatment will be excluded from the safety population. Moreover, patients who received any dose of study treatment but have no documented safety data will not be included in the safety analyses, because their inclusion would only serve to dilute percentages of patients with AEs or laboratory toxicities. Safety analysis will include patients recruited in the 3 arm and 4 arm design of the study. All safety analysis will be performed on the SS population.

5.2.1.4 Pharmacokinetic (PK) Population

The PK population consists of all patients who provide reportable plasma concentration and PK parameter data, and who have no significant protocol deviations or AEs that may impact on the PK. All PK analysis will be performed on the PK population.

5.2.1.5 Exploratory Biomarker Analysis Population

The exploratory biomarker analysis population consists of all patients who participated in the exploratory biomarker research. All exploratory biomarker analysis will be performed on the exploratory biomarker analysis population.

5.2.2 Protocol Deviations

Deviations that may be considered for exclusion or re-assignment of data in a PP analysis:

- Subjects who received the incorrect randomized therapy, these subjects should be included in the group according to the therapy actually received. If a subject is mis-randomised but still actually received the intended therapy they should not be excluded.

Deviations that may **not** lead to exclusion of data in a PP analysis:

- Subjects who deviate from entry criteria that were included to protect subject safety.
- Lack of compliance or dose reductions of therapy.
- Lack of compliance with the visit schedule.

5.3 Covariates and Subgroups

PFS will be assessed in all patients and separately within the PI3K-pathway activation subgroup of patients (defined as patients with activating PIK3CA mutations).

The randomisation of patients will be stratified by measurable disease (vs. non-measurable), and by sensitivity to prior endocrine therapy (sensitive versus resistant). These stratification factors will be used in the stratified log-rank test for the primary analysis for treatment comparison.

A covariate model (using demography parameters) will be added to the defined PK model. Modelling of the PK with pharmacodynamic endpoints, QTc, AEs and efficacy endpoints can then be undertaken as appropriate.

The following exploratory subgroup analysis will also be carried out:

1. Estimate the clinical activity (as measured by ORR, duration of response, and CBR) of Fulvestrant + AZD2014 (continuous schedule) in patients who switch to this treatment after progression on Fulvestrant + Everolimus.
2. Estimate the clinical benefit of Fulvestrant + AZD2014 relative to Fulvestrant + Everolimus or Fulvestrant alone:
    - in patients with and without aberrant activation of the PI3K/AKT/mTOR pathway
    - in patients with primary or secondary endocrine resistance

5.4 Missing Data

No imputation will be performed for missing data, with the exception of:

- As per the FACIT scoring guidelines, more than 80% of questions in a questionnaire must be completed for the questionnaire to be evaluable. If 80% or less of questions are completed, the questionnaire is not evaluable, and the data will be listed, but not included in any summaries or analyses.

Patients who are treated with the study drug but have no documentation for safety will not be included in safety analyses, because their inclusion would only serve to dilute percentages of patients with AEs or laboratory toxicities. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures.

5.5 Interim Analyses and Data Monitoring

5.5.1 Purpose of Interim Analyses

An interim analysis based on PFS is planned for the MANTA study to provide an early trigger for additional development work of AZD2014. The purpose of this detailed interim analysis is to provide data to allow an accelerated Phase III investment decision. AstraZeneca (AZ) intend, if AZD2014 in combination with Fulvestrant shows sufficient promise in this setting, to start Phase III trials without waiting for the final analysis of MANTA in order to make AZD2014 available to patients more quickly. A separate SAP will be created for interim analyses.

The study database will not be formally locked for the interim analysis; however, efforts will be made to ensure that the data is as complete and clean as possible. Estimated dates for the data cut off will be discussed with sites to allow pre-planning for data entry. Sites will be given 2 weeks from the data cut off to enter the final remaining data. An additional 6 weeks (dependent upon number and type of queries) will be allowed for production and resolution of critical data queries, prior to the final copy of the database being made and provided to the independent data monitoring committee (IDMC) independent statistician for analysis. At the time of the PFS interim analysis, sufficient progression events will have occurred for the comparison of AZD2014/Fulvestrant vs Fulvestrant alone to be appropriately sized for statistical comparison. NB: a test transfer of the database (with dummy treatment codes applied, and based on unclean data) will be provided to the CRO prior to this to enable pre-programming of the outputs required for the 'detailed interim analysis'. The same cut of data (i.e. database version) will be used for the PFS interim analysis as the detailed interim analysis.

5.5.2 Planned Schedule of Interim Analyses

The analysis will be carried out when approximately 40% of the number of events required for the final analysis have occurred in each of the Fulvestrant combined with AZD2014 vs Fulvestrant alone comparisons i.e. 52 events of PD per investigator assessment will have occurred in each of the Fulvestrant combined with AZD2014 vs Fulvestrant alone comparisons. The analysis is estimated to take place in Q2/Q3 2016.

5.5.3 Scope of Adaptations

There are no planned adaptations.

5.5.4 Stopping Rules

This initial PFS interim analysis will be performed by the MANTA IDMC statistician with the outcome being the provision of 'GO' or 'WAIT' to the study project manager and AZD2014 development team, using pre-specified criteria. These pre-specified criteria will be sent directly to the MANTA IDMC statistician and are not known to the MANTA Coordinating team. The outcome of this interim PFS analysis will not have an impact on the progress of the MANTA study unless the IDMC identify safety concerns (the safety data will be reviewed by the IDMC at the same time).

If the initial PFS interim analysis is positive (i.e. 'GO'), a further analysis will be triggered to allow acceleration of AZD2014 development ('Detailed interim analysis'). This analysis will be performed by an independent statistician at a CRO and the results reviewed by the MANTA study IDMC prior to release to AZ (AZ DMC). The detailed interim analysis, can be conducted prior to recruitment being completed on the study, but no results will be released to AZ until recruitment has completed. The detailed interim analysis will include efficacy and safety endpoints as well as generating the following HRs and confidence intervals (CIs):

- Fulvestrant + AZD2014 (continuous daily schedule) relative to Fulvestrant alone
- Fulvestrant + AZD2014 (intermittent schedule) relative to Fulvestrant alone
- Fulvestrant + AZD2014 (continuous daily schedule) relative to Fulvestrant + Everolimus
- Fulvestrant + AZD2014 (intermittent schedule) relative to Fulvestrant + Everolimus

If the result of the PFS interim analysis is 'WAIT' then no further analyses will be performed until the final analysis of the study.

5.5.5 Analysis Methods to Minimise Bias

Interim analysis will be conducted by an independent group to minimise bias.

5.5.6 Adjustment of Confidence Intervals (CIs) and p-values

For the planned non-binding interim analysis the intention is not to calculate any p-values (the HRs will instead be compared against pre-defined cut-offs). However, if any p-values are calculated then an alpha spending function like the Haybittle–Peto boundary will be used.

5.5.7 Interim Analysis for Sample Size Adjustment

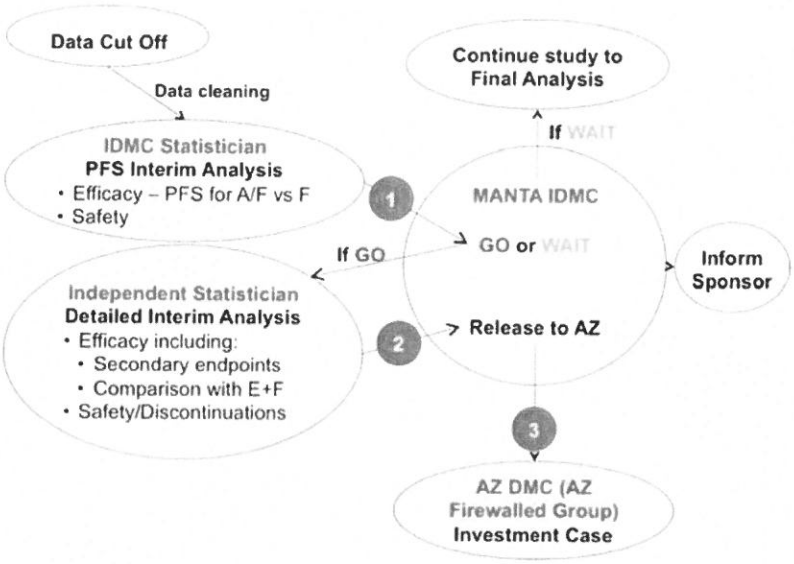
There is no plan to do any interim analysis for sample size adjustment.

5.5.8 Practical Measures to Minimise Bias

The independent group will carry out the interim analysis and the outcome of this interim analysis will be kept confidential with the independent group providing only the response of 'GO' or 'WAIT' to the AZD2014 development team.

AZ has provided the cut offs for the GO/WAIT decision directly to the IDMC statistician who will carry out the analysis and provide the MANTA IDMC with a GO/WAIT decision. In case of GO a detailed interim analysis will be performed by an independent CRO statistician. Pre-programming for this detailed interim analysis will be conducted up front by the independent group, but the final run will not be triggered until the 'GO' decision has been provided by the IDMC. The results will be reviewed by the IDMC prior to release to the study sponsor and a pre-defined AZ Firewalled Group (AZ DMC). This group will be constituted of senior expert staff at AZ deemed to be without direct involvement in trial conduct and able to make informed decisions. The group will be governed by a separate AZ DMC Charter, which will be shared with the IDMC and Queen Mary University of London (QMUL). The results will otherwise be kept confidential and will not be shared with the Trial Steering Group, Trial Management Group, Investigators etc. to minimise the impact of this analysis on conduct of the MANTA study.

	AZD2014	AZ DMC	QMUL	MANTA IDMC	CRO
High level interim analysis (IA) document	Write	Aware	Approve	Approve	Aware
AZ DMC Charter	Write	Approve	Aware	Aware	Aware
IA list of outputs	Write	Aware	Aware	Not required	Aware
IA SAP	Approve	Aware	Approve	Aware	Write
IA mock shells	Review	Not required	Not required	Not required	Produce
Blinded dry run of outputs	Review	Not required	Not required	Not required	Produce
Decision Criteria document	Write (stats)	Aware (approval by Governance)	Not required	Not required	Not req



5.5.9 Documentation of Interim Analyses

Data snapshots used in the interim analysis will be saved under the MANTA Data Management and Statistical Analysis folder on the centre for experimental cancer (CECM) Server. Only the CECM Database Programmer will have access to the folder holding the interim analysis snapshot. A copy of the data snapshot will also be saved by the independent statistician at their local institution servers along with copies of the programming code used and reports produced. These will be transferred to the MANTA Coordinating team at the end of the study for archiving along with the main study trial master file (TMF).

5.6 Multi-Centre Studies

This is a phase II trial with more than 70 recruiting centres. It is not expected that centre will have any effect to the primary outcome. However, geographic region/country may have some effect on the primary outcome PFS. This study is not designed to ascertain any regional effect and hence exploratory analysis may be done on the primary endpoint to see any regional variation of the outcome.

5.7 Multiple Testing

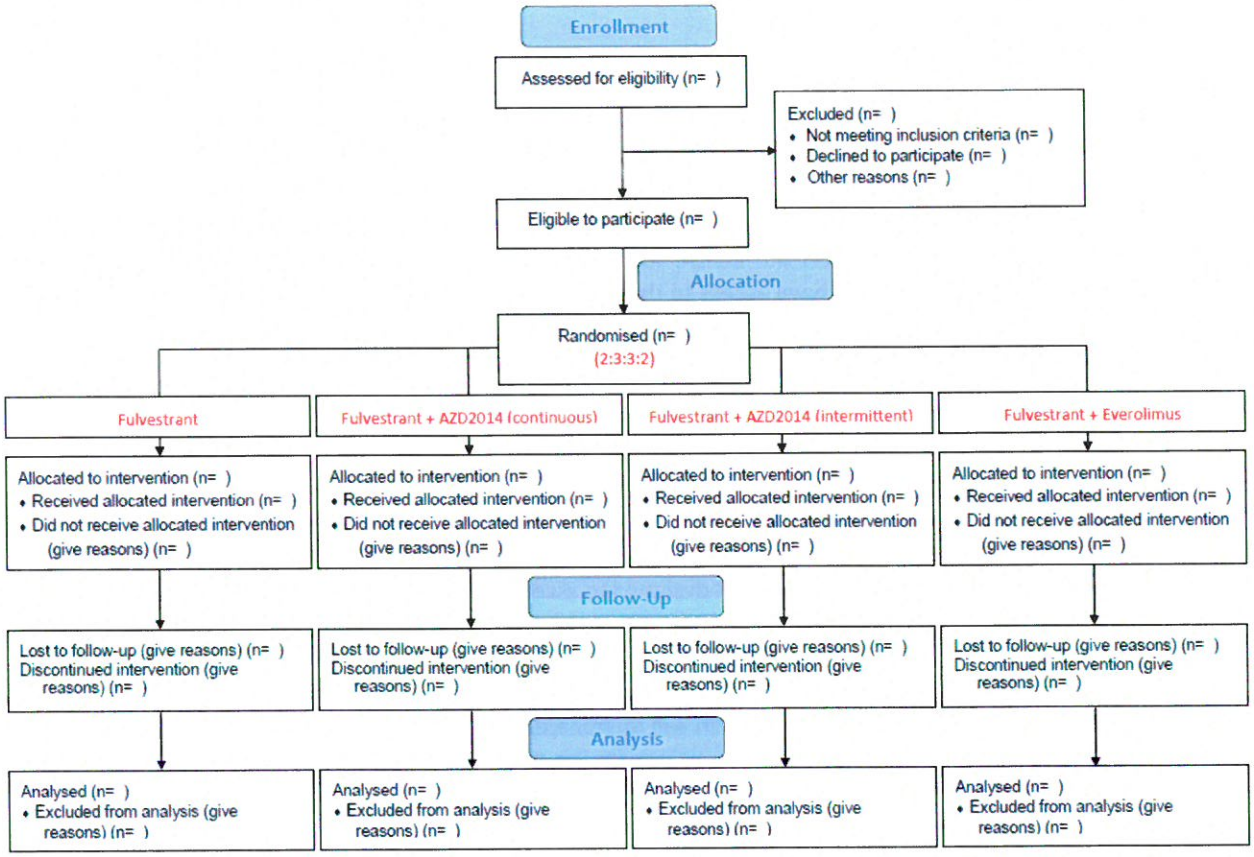
No adjustment for multiple comparison will be done except for the primary endpoint PFS (Haybittle-Peto adjustment will be done to the p-values for the primary endpoint if any p-values are calculated at interim analysis).

6 Summary of Study Data

Study data will be summarised using appropriate summary statistics (i.e. mean, standard deviation, median, and range for continuous variables, and number and proportion of patients for categorical variables). Summaries will be presented overall and by treatment arm, for the SS population. The baseline value of any variable will be defined as the last available value prior to the first administration of study treatment.

6.1 Subject Disposition

A CONSORT diagram will be produced as follows (as applicable):


Enrollment
Assessed for eligibility (n=)
Excluded (n=)
• Not meeting inclusion criteria (n=)
• Declined to participate (n=)
• Other reasons (n=)
Eligible to participate (n=)
Allocation
Randomised (n=)
(2:3:3:2)
Fulvestrant
Fulvestrant + AZD2014 (continuous)
Fulvestrant + AZD2014 (intermittent)
Fulvestrant + Everolimus
Allocated to intervention (n=)
• Received allocated intervention (n=)
• Did not receive allocated intervention (give reasons) (n=)
Allocated to intervention (n=)
• Received allocated intervention (n=)
• Did not receive allocated intervention (give reasons) (n=)
Allocated to intervention (n=)
• Received allocated intervention (n=)
• Did not receive allocated intervention (give reasons) (n=)
Allocated to intervention (n=)
• Received allocated intervention (n=)
• Did not receive allocated intervention (give reasons) (n=)
Follow-Up
Lost to follow-up (give reasons) (n=)
Discontinued intervention (give reasons) (n=)
Lost to follow-up (give reasons) (n=)
Discontinued intervention (give reasons) (n=)
Lost to follow-up (give reasons) (n=)
Discontinued intervention (give reasons) (n=)
Lost to follow-up (give reasons) (n=)
Discontinued intervention (give reasons) (n=)
Analysis
Analysed (n=)
• Excluded from analysis (give reasons) (n=)
Analysed (n=)
• Excluded from analysis (give reasons) (n=)
Analysed (n=)
• Excluded from analysis (give reasons) (n=)
Analysed (n=)
• Excluded from analysis (give reasons) (n=)

The number of patients who are randomised will be tabulated by study site. Patient disposition will be tabulated, and reasons for premature discontinuation will be summarised.

6.2 Protocol Deviations

Eligibility exceptions and protocol deviations will be summarised.

6.3 Demographic and Baseline Variables

Demographic and baseline characteristics and stratification factors (age; body-mass index [BMI]; country; Eastern Cooperative Oncology Group (ECOG) performance status; measurable disease at randomisation; sensitivity to endocrine treatment at randomisation; previous adjuvant/neoadjuvant chemotherapy; previous metastatic chemotherapy; number of previous endocrine treatment) will be summarised.

6.4 Concurrent Illnesses and Medical Conditions

All AEs and SAEs will be coded according to the latest available Medical Dictionary for Regulatory Activities (MedDRA) version. The Chief Investigator may wish to group MedDRA codes further into more clinically meaningful groups for analysis and interpretation. Any grouping of toxicity codes will be signed off by the Chief Investigator.

6.5 Prior and Concurrent Medications

Prior and concomitant medications will be summarised in terms of frequency. Medication will be coded using Systematized Nomenclature of Medicine (SNOMED).

Prior medications are defined as any medications (including prescription medications and over-the-counter preparations) used by the patient prior to the time of providing written informed consent. Concomitant medications are defined as any medications (including prescription medications and over-the-counter preparations) used by the patient from the time of providing written informed consent, during the study, and up to the end of treatment visit.

6.6 Treatment Compliance

Treatment compliance will be presented in terms of:

1. Frequency and percentage of patients missing at least one dose.
2. Median and interquartile range (IQR) of the number of days of investigational medicinal product (IMP) missed (based on all patients who missed at least one dose of IMP).
3. Percentage of days of IMP missed (as a percentage of total number of days patients are on treatment in each arm).
4. Frequency and percentage of patients having at least one occasion of dose reduction on IMP.
5. Frequency and percentage of patients discontinuing IMP.
6. Frequency and percentage of patients coming off study due to disease progression (deaths and withdrawals).

7 Efficacy Analyses

7.1 General Principles

Efficacy data will be summarised using appropriate summary statistics (i.e. mean, standard deviation, median, and range for continuous variables, and number and proportion of patients for categorical variables). CIs will be calculated as appropriate. Summaries will be presented overall and by treatment arm, for the ITT population. The baseline value of any variable will be defined as the last available value prior to the first administration of study treatment.

The primary comparison will be between Fulvestrant + AZD2014 (continuous daily schedule) relative to Fulvestrant alone. Any comparison with Fulvestrant + Everolimus or with intermittent dosing of AZD2014 will be secondary.

The efficacy endpoints will be analysed according to ITT analysis based on all patients (including the additional patients from the three-arm version of the trial). Sensitivity analysis will be carried out by separately analysing those patients in the four-arm part of the study. The secondary efficacy analyses relating to ORR and CB will however be according to PP analysis.

A one-sided 5% significance level test will be used to assess the statistical significance of the treatment group differences in the efficacy outcome variables. The HR for treatment will be estimated (a HR less than 1 will favour AZD2014+Fulvestrant). The p-value will be calculated such that the p-value is less than 0.05 if AZD2014+Fulvestrant is better than control and the p-value is greater than 0.05 if control is better than AZD2014 +Fulvestrant i.e. (two-sided p value)/2 or 1-(two-sided p-value/2). If we observe a result that gives $p<0.025$ (1-sided) such a result would be regarded as being statistically significant at conventional levels. CIs will be presented as 2-sided 90% CI (equivalently 1-sided 95% CI) to match with the 5% 1-sided significance level, and as conventional 2-sided 95% CI (i.e. to assess how results would be interpreted in relation to standard confirmatory significance levels). Only 90% CIs will be presented for the interim analysis results.

7.2 Primary Efficacy Analysis

7.2.1 Progression-Free Survival (PFS)

Kaplan-Meier (K-M) methodology will be used to estimate the median PFS for each arm. The median PFS will be estimated with 95% CI, and the K-M curve will be plotted. The K-M curve with stratified log-rank test (stratified by baseline stratification factors) will be used as the primary analysis for treatment comparison.

The effect of treatment will be estimated by the HR together with its corresponding 90% and 95% CIs and p-value. The log-rank method to be used to estimate the HR is that in Freedman (1982) [1] and Schoenfield (1981) [2].

The proportional hazards assumption will be examined using Schoenfield residuals. Statistical assumptions will be assessed and additional analyses may be considered if these assumptions do not hold.

The stratification factor of sensitivity to endocrine treatment was incorrectly categorised for some patients. As a result, the primary endpoint PFS will be analysed based on both the incorrect as well as the correct classification to see the sensitivity of the results at final analysis. However, this misclassification does not have any impact on the safety data.

PFS will be assessed in all patients and separately within the PI3K-pathway activation subgroup of patients (defined as patients with activating PIK3CA mutations).

7.3 Secondary Efficacy Analyses

7.3.1 Objective Response Rate (ORR)

An estimate of the ORR and 95% CIs (Clopper and Pearson 1934 [3]) will be calculated for each treatment arm. CIs for the difference in ORR (Santner and Snell 1980 [4]; Berger and Boos 1994 [5]) will be calculated.

The relative benefit (i.e. benefit ratio) of response (treatment: control) will be reported along with the associated 95% CI based on log-binomial regression model.

For patients with an objective response, median duration of response will be summarised by treatment arm and compared. Methods for handling censoring and for analysis are the same as those described for PFS.

7.3.2 Clinical Benefit Rate (CBR)

An estimate of CBR and 95% CIs (Clopper and Pearson 1934 [3]) will be calculated for each treatment arm. CIs for the difference in CBR (Santner and Snell 1980 [4]; Berger and Boos 1994 [5]) will be calculated.

The relative benefit (i.e. benefit ratio) of response (treatment: control) will be reported along with the associated 95% CI based on log-binomial regression model.

For patients with a CB, median duration of CB will be summarised by treatment arm and compared. Methods for handling censoring and for analysis are the same as those described for PFS.

7.3.3 Overall Survival (OS)

K-M methodology will be used to estimate the median OS for each arm. The median OS will be estimated with 95% CI, and the K-M curve will be plotted. The K-M curve with stratified log-rank test (stratified by baseline stratification factors) will be used for treatment comparison.

The effect of treatment will be estimated by the HR together with its corresponding 95% CI and p-value. The log-rank method to be used to estimate the HR is that in Freedman (1982) [1] and Schoenfield (1981) [2].

The proportional hazards assumption will be examined using Schoenfield residuals. Statistical assumptions will be assessed and additional analyses may be considered if these assumptions do not hold.

7.4 Exploratory Efficacy Analyses

7.4.1 Clinical Activity

Clinical activity is measured by ORR and duration of response, and CBR as defined in Sections 7.3.1 and 7.3.2 respectively. The clinical activity of Fulvestrant + AZD2014 (continuous schedule) patients who switch to this treatment after progression on Fulvestrant + Everolimus will be assessed.

7.4.2 Clinical Benefit

Clinical benefit is measured by PFS as defined in Section 7.2.1 . The clinical benefit of Fulvestrant + AZD2014 relative to Fulvestrant + Everolimus or Fulvestrant alone will be assessed:

- in patients with and without aberrant activation of the PI3K/AKT/mTOR pathway
- in patients with primary or secondary endocrine resistance

8 Safety Analyses

Safety data will be summarised using appropriate summary statistics (i.e. mean, standard deviation, median, and range for continuous variables, and number and proportion of patients for categorical variables). Summaries will be presented overall and by treatment arm, for the SS population. The baseline value of any variable will be defined as the last available value prior to the first administration of study treatment.

8.1 Extent of Exposure

Exposure data will be summarised, indicating total exposure to study drug and total time on study, as well as the number of any dose interruptions, reductions and dose intensity i.e. relative dose intensity (RDI) and percentage intended dose (PID).

RDI is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation. PID is the percentage of the actual dose delivered relative to the intended dose through to progression or treatment completion. Both will be derived using the date of objective disease progression as defined by RECIST using the investigator site assessments. RDI and PID will be defined as follows:

- RDI = 100% * d/D, where d is the actual cumulative dose delivered up to the earlier of progression (or a censoring event) or the actual last day of dosing and D is the intended cumulative dose up to the earlier of progression (or a censoring event) or the actual last day of dosing.
- PID = 100% * d/D, where d is the actual cumulative dose delivered up to progression (or a censoring event) and D is the intended cumulative dose up to progression (or a censoring event). D is the total dose that would be delivered, if there were no modification to dose or schedule.

8.2 Adverse Events (AEs)

AEs, irrespective of relatedness, will be summarised. Verbatim descriptions of treatment-emergent AEs will be mapped to the appropriate thesaurus terms and summarised by mapped MedDRA term, and National Cancer Institute (NCI) CTCAE grade. For each patient's AE, the maximum severity reported will be used in the summaries. SAEs, including deaths, will be summarised separately. Specifically, the following descriptive statistics will be generated.

1. Incidence of SAEs
2. Incidence of grade 3 and 4 AEs (CTCAE, version 4.0.3)
3. Incidence of all AEs of all grades
4. Incidence of the following selected AEs (any grade):
    - Hyperglycaemia
    - Diarrhoea
    - Stomatitis
    - Rash
    - Interstitial pneumonitis
    - Fatigue
    - T-Wave changes
5. AEs leading to discontinuation of the study medication

8.3 Deaths, Serious Adverse Events (SAEs) and other Significant AEs

All deaths, SAEs and other significant events will be summarised in line listings. SAEs will be reconciled with the AEs.

8.4 Pregnancies

Not applicable – all eligible patients are postmenopausal.

8.5 Clinical Laboratory Evaluations

Laboratory data will be tabulated, with values outside normal ranges identified and summarised by NCI CTCAE (Version 4.0.3) grade. Normal ranges for each site will be used as reference for that site's biochemistry results. Bart's ranges will be used as reference for all haematology results, and also for any sites with missing biochemistry ranges (due to the site not having their own ranges or any other

reason for missing ranges). The worst condition for each patient during the entire treatment will be reported.

8.6 Other Safety Measures

8.6.1 Vital Signs

Changes in vital signs data will be summarised by scheduled measurement time. Vital signs will include height (cm), weight (kg), temperature (degrees Celsius), blood pressure, and heart rate.

8.6.2 Electrocardiogram (ECG) Changes

Overall evaluation of ECG will be listed.

QTc will be calculated by Fridericia's (QTcF) formulae as follows:

$$QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

, if QT & RR is measured in msec.

The baseline value for each parameter is the last value observed prior to first dosing day on Day 1 Cycle 1. The change from baseline is defined as the post-baseline value minus the baseline value. There will not be any imputation for missing values.

The number and percentage of patients with increases of QTcB and QTcF of > 60msec from baseline, and QTcB and QTcF values of > 500msec will be produced.

9 Pharmacokinetics (PKs)

AZD2014 plasma concentrations and all other relevant associated data (e.g. sampling and dosing time information) taken following the first AZD2014 dose and following multiple dosing will be merged with similar data from other studies in order to estimate appropriate AZD2014 PK parameters for each patient using non-linear mixed effects population modelling techniques. PK analysis may be reported separately for each of the AZD2014 schedules.

PK parameters where possible will include plasma drug clearance (CL/F), estimated maximum drug concentration (Cmax), elimination half-life (t1/2) and volume of distribution (Vss/F). A covariate model (using demography parameters) will be added to the defined PK model. Modelling of the PK with pharmacodynamic endpoints, QTc, AEs and efficacy endpoints can then be undertaken as appropriate. The results of any such analyses will be reported separately to the CSR for this study.

Where possible the PK parameter Css,min will be determined for Fulvestrant in each treatment arm from the pre-dose plasma samples taken just before the Fulvestrant injections on Cycle 2 Day 1 and Cycle 3 Day 1. These values will be compared to reported trough concentrations from patients receiving Fulvestrant 500mg as a single agent in other studies. The results of any such analyses will be reported separately to the CSR for this study.

The PK analysis will be reported separately to the CSR.

10 Other Analyses

10.1 Patient Reported Outcomes (PRO)

The TOI, overall HRQOL score (from the total FACT-G-AA-ES scales), and individual subscale scores from the 6 subscales (PWB, SWB, EWB, FWB, AAS, ESS-23) will be summarized over time using raw score or pro-rated scores of missing data and change from baseline and percent change from baseline.

Note for reviewer: due to missing data these summary should be taken very cautiously.

11 Figures

K-M curves will be plotted for the PFS, OS, duration of response, and duration of CB analyses.

12 Reporting Conventions

P-values ≥0.01 will be reported to 2 decimal places; p-values less than 0.01 will be reported as "<0.01". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 2 decimal places.

13 Technical Details

Analysis will be conducted using Stata v 13 (or subsequent versions). A second statistician will independently double check the statistical codes for the main endpoints of analysis following our Statistical standard operation procedure (SOP).

This SAP is based on MANTA Protocol: Master Version 5.0 dated 2nd March 2016. All programs will be stored in the *G:\Experimental Cancer Medicine\Statistics\Inhouse Unblinded\MANTA* folder until the end of the study at which point they will be merged with the TMF for archiving.

14 Summary of Changes to the Protocol

The following changes have been made since the signing of the MANTA protocol Master Version 5.0 dated 2nd March 2016:

1. The primary efficacy endpoint will be analysed once the event count of 130 PFS or death events has been observed for the study (including all patients from the 3 and 4 arm schedules). Sensitivity analysis will then be performed to see if there are relevant differences between excluding and including those patients in the 3 arm schedule. If no differences exist, then the trial final analyses will be performed at the end of the study, with no additional PFS analysis. If there is a significant difference, additional PFS analysis will be required once 130 events have been observed in the 4 arm schedule only. Adjustment for type 1 error may be required for this potential additional analysis.
2. The protocol Section 10.4.1 incorrectly states: "PFS is defined as the time from the date of randomisation to disease progression or relapse (using RECIST, Version 1.1) or death on study from any cause, whichever occurs first." However, relapse should not be considered in the definition of PFS. Only tumour progression based on investigator assessment (using RECIST v1.1) or death from any cause, whichever occurs first will be considered as events in the definition of PFS. This has been updated in all applicable sections of the above SAP text.
3. The protocol includes secondary objectives related to assessment of scans by an IRF. Instead, a comparison will be made during the study to determine if there is a significant difference between the investigator and IRF assessments. If no difference exists, then no analyses will be performed based on IRF assessment. If there is a significant difference, the IRF assessment will be the basis for a secondary PFS analysis and also for secondary analysis of all other efficacy endpoints. This has been updated in all applicable sections and also specified in Section 3.4.1.1 of this SAP.

4. The protocol includes the secondary endpoint of change in tumour size at 16 weeks (to assist with assessing clinical activity). This analysis does not seem necessary for the final analysis of this trial and has therefore been removed. This has been updated in all applicable sections of the above SAP text.
5. The protocol Section 4.2 incorrectly states that duration of response is defined as the time from first documentation of complete or partial response to disease progression. However, it should be "Duration of response, defined as the time from randomisation to disease progression based on investigator assessment using RECIST v1.1, or death from any cause, whichever occurs first, in patients with objective response". This has been updated in all applicable sections of the above SAP text.
6. The protocol Section 4.2 incorrectly states that duration of CB is defined as the time from randomisation to disease progression in patients with CB. However, it should be "Duration of CB, defined as the time from randomisation to disease progression based on investigator assessment using RECIST v1.1, or death from any cause, whichever occurs first, in patients with CB". This has been updated in all applicable sections of the above SAP text.
7. The protocol Section 10.4.2 states the relative risk (for objective response and CB) will be calculated based on the logistic regression model. However, the log-binomial regression model will be used with the purpose of providing the relative benefits directly as logistic regression provides the odds ratio. This has been updated in all applicable sections of the above SAP text.

15 References

1. Freedman, L. S. 1982. Tables of the number of patients required in clinical trials using the logrank test. Statistics in Medicine 1: 121–129.
2. Schoenfeld, D. 1981. The asymptotic properties of nonparametric tests for comparing survival distributions. Biometrika 68: 316–319.
3. Clopper, C. J., and E. S. Pearson. 1934. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 26: 404-413.
4. Santner, T. J. and Snell, M. K. (1980). Small-sample confidence intervals for P1 -P2 and P1/P2 in 2 x 2 contingency tables. Journal of the American Statistical Association 75, 386-394.
5. Berger, R. L. and Boos, D. D. (1994). P values maximized over a confidence set for the nuisance parameter. Journal of the American Statistical Association 89, 1012-1016.