PROTOCOL TITLE:

A phase Ib trial of fulvestrant, palbociclib (CDK4/6 inhibitor) and erdafitinib (JNJ-42756493, pan-FGFR tyrosine kinase inhibitor) in ER+/HER2–/*FGFR*-amplified metastatic breast cancer (MBC)

Protocol Number	VICCBRE16126 (NCT03238196)
Protocol Chair	PI Name: Vandana Abramson, MD Institution: Vanderbilt-Ingram Cancer Center (VICC) Address: 2200 Pierce Ave. 777 PRB, Nashville, TN 37232 Phone: 615-936-8422 Fax: 615-343-7602 Email: vandana.abramson@vumc.org
Co-Investigators	
Medical Oncology	Komal Jhaveri, MD – Memorial Sloan Kettering Cancer Center (MSKCC) Hope Rugo, MD – University of California San Francisco (UCSF) Erica Stringer Reasor, MD – University of Birmingham Alabama (UAB) Adam Brufsky, MD – University of Pittsburgh Medical Center (UPMC)
Pathology	Melinda Sanders, MD Melinda.sanders@vumc.org Vanderbilt-Ingram Cancer Center (VICC)
Laboratory Correlatives	Komal Jhaveri, MD – Memorial Sloan Kettering Cancer Center (MSKCC) jhaverik@mskcc.org Carlos L. Arteaga, MD - UT Southwestern (UTSW) Carlos.arteaga@utsouthwestern.edu
Statistician	Fei Ye, PhD Fei.ye@vumc.org Vanderbilt-Ingram Cancer Center (VICC)
Supporters	Pfizer Janssen Research and Development
Funding Mechanism	ASPIRE Breast Cancer Research Awards Program
Coordinating Center/ Sponsor	Vanderbilt-Ingram Cancer Center (VICC) Multi-Institutional Coordinating Office Fax: (615) 875-0040

Email: Coordinating.center@vumc.org

Study Liaison:
Jannine Hewitt, RN
Jannine.hewitt@vumc.org

Investigational New Drug (IND) Number 134219

- Protocol Revision Record -

Original Protocol: 10/13/16

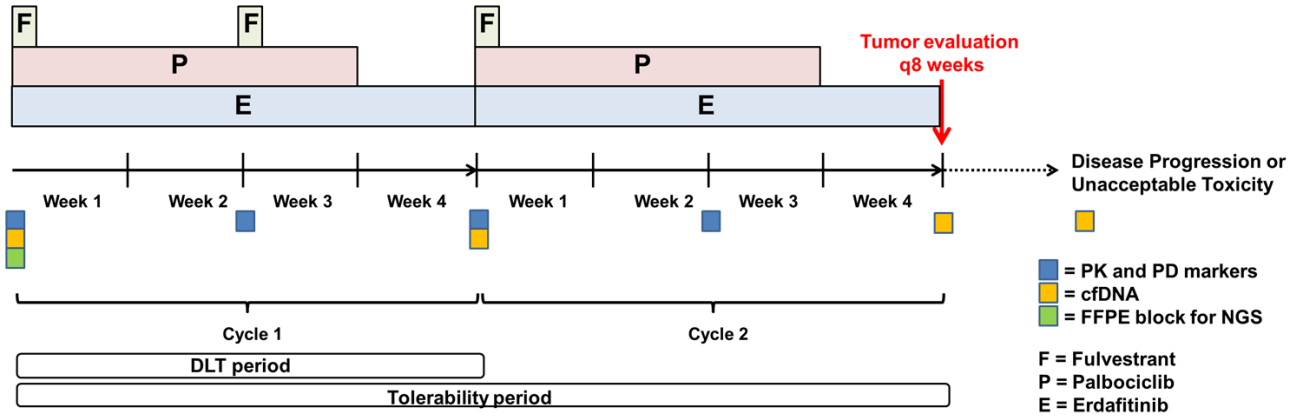
Amendment #1:	07/17/2017
Amendment #2:	08/15/2017
Amendment #3:	01/09/2018
Amendment #4:	11/26/2019
Amendment #5:	04/08/2020
Amendment #6:	11/04/2021

Table of Contents

SCHEMA **5**
PROTOCOL SYNOPSIS **6**
1. STUDY DESIGN/SUMMARY **12**
2. OBJECTIVES AND ENDPOINTS **13**
3. BACKGROUND **14**
3.1 Estrogen receptor-positive (ER+) Breast Cancer 14
3.2 Endocrine Therapy and CDK4/6 Inhibition 15
3.3 Fibroblast Growth Factor Receptor-1 (FGFR1) in ER+ Breast Cancer 17
3.4 FGFR and CDK4/6 Inhibition in ER+ Breast Cancer - Preliminary Data 19
3.5 Rationale 22
3.6 Correlative Science Background 22
4. PARTICIPANT SELECTION **23**
4.1 Inclusion Criteria 24
4.2 Exclusion Criteria 26
4.3 Inclusion of Underrepresented Populations 27
5. REGISTRATION PROCEDURES **28**
5.1 Guidelines for VICC and TBCRC Institutions 28
6. STUDY CALENDAR **30**
7. TREATMENT PLAN **33**
7.1 Overview 33
7.2 Screening Phase 33
7.3 Agent Administration 33
7.4 Definition of Dose-Limiting Toxicity (DLT) 35
7.5 Definition of Maximum Tolerated Dose (MTD) 38
7.6 Concomitant Treatment and Supportive Care Guidelines 39
7.7 Duration of Therapy 40
7.8 Duration of Follow-Up 40
7.9 Criteria for Removal from Study 40
7.10 Discontinuation of Treatment 40
7.11 Replacement of Patients Who Discontinue Early 41
7.12 Withdrawal from Study 41
8. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS **41**
8.1 Erdafitinib 41
8.2 Fulvestrant 45
8.3 Palbociclib 45
8.4 Palbociclib and Erdafitinib Dose Modifications and Management of Toxicities 46
8.5 Special Considerations 52
9. DRUG FORMULATION/STORAGE/SUPPLY **53**
9.1 Erdafitinib 53
9.2 Fulvestrant 54
9.3 Palbociclib 55
9.4 Drug Accountability 57

10. CORRELATIVE/SPECIAL STUDIES 58
10.1 Overview 58
10.2 Blood Samples for Pharmacodynamic Assessments 60
10.3 Blood Samples for cfDNA 60
10.4 Blood Samples for NGS control 61
10.5 Tissue Samples 61
10.6 Pharmacokinetics 65
10.7 Genetic Testing 67
11. SPECIMEN BANKING 68
12. MEASUREMENT OF EFFECT 69
12.1 Definitions 69
12.2 Disease Parameters 69
12.3 Response Criteria 71
12.4 Duration of Response 73
13. ADVERSE EVENT REPORTING REQUIREMENTS 73
13.1 General 73
13.2 Definitions 73
13.3 Reporting Procedures 75
14. DATA AND SAFETY MONITORING 80
14.1 Data Management and Reporting 80
14.2 Data Handling and Record Keeping 81
14.3 Meetings 82
14.4 Monitoring 82
15. REGULATORY CONSIDERATIONS 84
15.1 Pre-Study Documentation 84
15.2 Protocol Review and Amendments 84
15.3 Informed Consent 85
15.4 Confidentiality and Disclosure 85
15.5 Records Retention 86
15.6 Study Termination 86
15.7 Ethics and GCP 87
15.8 Compliance with Trial Registration and Results Posting Requirements 87
16. MULTI-CENTER GUIDELINES 87
16.1 Study Documentation 87
16.2 Records Retention 88
16.3 Publication 88
17. STATISTICAL CONSIDERATIONS 88
17.1 Study Design/ Endpoints 88
17.2 Sample Size and Statistical Analysis 88
17.3 Reporting and Exclusions 92
18. REFERENCES 93
19. MEDICATIONS TO BE USED WITH CAUTION 96

SCHEMA


F
F
F
P
P
E
E
Tumor evaluation
q8 weeks
Week 1
Week 2
Week 3
Week 4
Week 1
Week 2
Week 3
Week 4
Disease Progression or
Unacceptable Toxicity
= PK and PD markers
= cfDNA
= FFPE block for NGS
Cycle 1
Cycle 2
DLT period
Tolerability period
F = Fulvestrant
P = Palbociclib
E = Erdafitinib

PROTOCOL SYNOPSIS

Sponsor	Vanderbilt-Ingram Cancer Center
Protocol Title	A phase Ib trial of fulvestrant, palbociclib (a CDK4/6 inhibitor) and erdafitinib (JNJ-42756493, a pan-FGFR tyrosine kinase inhibitor) in ER+/HER2–/*FGFR*-amplified metastatic breast cancer (MBC)
Protocol Number	VICCBRE16126 (NCT03238196)
Phase of Development	Phase Ib
Investigational Product and Mechanism	• Erdafitinib, an oral pan-FGFR inhibitor (please note that the combination of erdafitinib, palbociclib and fulvestrant is also investigational)
Non-Investigational Products and Mechanism	• Palbociclib, a CDK4/6 inhibitor • Fulvestrant, a selective estrogen-receptor downregulator (SERD)
Treatment Schedule Dose/Route	• Erdafitinib (4 – 8 mg) mg PO daily • Palbociclib 125 mg PO daily from day 1 – 21, every 28 days • Fulvestrant 500 mg IM once every 28 days
Objectives	<u>Primary Objectives</u> • To determine the safety and tolerability of fulvestrant, palbociclib and erdafitinib in patients with ER+/HER2-/*FGFR*-amplified MBC. <u>Secondary Objectives</u> • To determine the anti-tumor effect of fulvestrant, palbociclib and erdafitinib in patients with ER+/HER2-/*FGFR*-amplified MBC. • Pharmacokinetic assessments of erdafitinib <u>Correlative Objectives</u> • To determine the therapeutic predictive role of *FGFR1-4, CCND1-2, CDK4* and *CDK6* amplifications, and *RB1* and *ESR1* mutations on clinical outcome • To determine if the *FGFR1* amplification levels by FISH and cfDNA is an early surrogate of response • To determine if the cfDNA results at disease progression show new genomic alterations potentially associated with resistance to CDK4/6 and FGFR inhibition • To determine pharmacodynamic biomarkers of FGFR inhibition
Endpoints	<u>Primary Endpoint</u> • Assessment of DLT during the first 4 weeks of treatment (cycle 1) • Determination of MTD <u>Secondary Endpoints</u> • Progression Free-Survival (PFS) • Overall response rate (ORR) • Clinical benefit rate (CBR; complete response + partial response + stable disease without disease progression at 6 months) • Pharmacokinetic assessments of erdafitinib <u>Correlative Endpoints</u>

	• *FGFR1* fluorescence in situ hybridization (FISH) • Next Generation Sequencing (NGS) of baseline or archival tumor specimen • Plasma tumor cell free [cf] DNA at baseline, at 4 weeks and at disease progression • Serial measurements of serum phosphate, calcium, vitamin D, parathyroid hormone (PTH), FGF23, sFGFR2, sFGFR3 and sFGFR4
Trial Design	This is an open-label, multi-institution, phase Ib trial that evaluates the safety, tolerability, and anti-tumor activity of fulvestrant, palbociclib with erdafitinib in patients with ER+/HER2-/*FGFR*-amplified metastatic breast cancer (MBC).
Number of Patients	• Minimum: 26 patients • Maximum: 35 patients
Participating Institutions	• Vanderbilt-Ingram Cancer Center (Coordinating Center) • TBCRC (4 centers)
Duration of Therapy	In the absence of treatment delays due to adverse events, treatment will continue until: • Disease progression • Inter-current illness that prevents further administration of treatment • Unacceptable adverse event(s) • Patients decides to withdraw from the study • Significant patient non-compliance with protocol
Duration of Follow-up	• Patients will be followed every three months until disease progression, or until death from any cause (whichever occurs first) • Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related adverse events to Grade 2 or lower • Patients continuing fulvestrant who have discontinued erdafitinib or palbociclib for any reason other than disease progression will be followed until disease progression

Patient Selection	Inclusion Criteria (abbreviated) • Patients (female or male) must provide informed written consent and must complete all screening assessments as outlined in the protocol • Patients must be able to swallow and retain oral medication • Patients must be ≥ 18 years of age • Female patients of no childbearing potential. Patients must be post-menopausal by at least one of the following criteria prior to enrollment: o Subjects at least 60 years of age; OR o Subjects under 60 years of age and naturally (spontaneous, no alternative pathologic or physiological cause) amenorrhea for at least 12 months; OR o Medical ovarian failure confirmed by follicle-stimulating hormone (FSH) and estradiol levels in the post menopausal range per local institutional normal range; OR o Prior bilateral oophorectomy; OR o Prior radiation castration with amenorrhea for at least 6 months; OR o Treatment with a luteinizing hormone-releasing hormone (LH-RH) agonist (such as goserelin acetate or leuprolide acetate) is permitted for induction of ovarian suppression as long as it has been initiated at least 28 days prior to study enrollment • ECOG performance status 0 - 1 • Clinical stage IV or inoperable locoregional recurrent invasive mammary carcinoma that is: o ER+ and/or PgR+ (≥ 1% positive stained cells) by immunohistochemistry (IHC) o HER2-negative (by IHC or FISH, per ASCO guidelines) o *FGFR1 - 4*amplified (may be determined by local assessment through either targeted capture next generation sequencing (NGS), plasma tumor cell free [cf] DNA or FISH) in 50% of the patients

participating in the expansion cohort of the trial (not necessary in the escalation cohort)

- Evaluable (may have either measurable or non-measurable disease)

- Patients must have available tissue (archival formalin-fixed paraffin embedded (FFPE) blocks or fresh frozen biopsy from primary tumor or metastatic tumor biopsy) for correlative studies. Tissue source needs to be located and available at the time of registration (tissue needs to be submitted within 3 weeks of study initiation). Patients will not be able to start study drugs without tissue availability. Submission of tissue can be waived, if approved by the Study Chair in case of extraordinary/ catastrophic circumstances.

- Current use of any of the drugs listed on the Cautionary Concomitant Medications list has to be approved by the Study Chair

- Patient must have had at least one line of therapy in the metastatic setting

- Patients must have adequate hematologic, hepatic, and renal function. All laboratory tests must be obtained within 2 weeks from study entry. These include:
  - ANC ≥ 1,500/mm^3
  - Platelet count ≥ 100,000/mm^3
  - HgB ≥ 9.0 g/dL
  - Creatinine clearance ≥ 40 mL/min/1.73 m^2
  - SGOT, SGPT ≤ 2.5 x ULN if no liver metastasis present
  - SGOT, SGPT ≤ 4 x ULN if liver metastasis present
  - Albumin ≥ 2.0 g/dL
  - Total serum bilirubin ≤ 1.5 x ULN (≤ 3 x ULN or direct bilirubin ≤ 1.5 x ULN if known Gilbert's syndrome)
  - Potassium within institutional normal limits
  - Phosphorus ≤ institutional upper limit of normal

<u>Exclusion Criteria (abbreviated)</u>

- Prior use of an FGFR inhibitor

- More than 2 lines of chemotherapy in the metastatic setting. There is no limit on endocrine therapy lines

	• Radiation therapy ≤ 2 weeks prior to study entry. Patients who have received prior radiotherapy must have recovered from toxicity (≤ grade 1) induced by this treatment (except for alopecia) • Prior cancer therapy (except for endocrine therapy) must have been discontinued for 1 week prior to initiation of study drugs • Concurrent anti-cancer therapy other than the ones specified in the protocol is not permitted during study participation. Bisphosphonates or denosumab are allowed • Major surgery within 4 weeks of enrollment • Herbal preparations are not allowed throughout the study, and must be discontinued at least 14 days prior to initiation of study treatment • Any corneal or retinal abnormality likely to increase the risk of eye toxicity, such as: o Current corneal pathology such as keratitis, keratoconjunctivitis, keratopathy, corneal abrasion, inflammation or ulceration o Uncontrolled glaucoma despite standard of care therapy o Diabetic retinopathy with macular edema o Known active wet, age-related macular degeneration (AMD) o Known central serous retinopathy (CSR) or retinal vascular occlusion (RVO) • Uncontrolled intercurrent illness including, but not limited to: o Malabsorption syndrome significantly affecting gastrointestinal function o Ongoing or active infection requiring antibiotics/ antivirals o Impairment of lung function (COPD > grade 2, lung conditions requiring oxygen therapy) o Symptomatic congestive heart failure (class III or IV of the New York Heart Association classification for heart disease) o Unstable angina pectoris, angioplasty, stenting, or myocardial infarction within 6 months o Clinically significant cardiac arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia that is symptomatic or requires treatment [National Cancer Institute -

	Common Terminology Criteria for Adverse Events, Version 4.03, grade 3] ○ QTcF ≥ 480 msec on screening EKG ○ Known history of QT/QTc prolongation or Torsades de Pointes (TdP) ○ ST depression or elevation of ≥ 1.5 mm in 2 or more leads ○ Diarrhea of any cause ≥ CTCAE grade 2 that does not resolve within a few days under adequate treatment ○ Psychiatric illness/social situations that would compromise patient safety or limit compliance with study requirements including maintenance of a compliance/pill diary ○ Symptomatic brain metastases (patients with a history of brain metastases must be clinically stable for more than 4 weeks from completion of radiation treatment and off steroids) ○ Known history of chronic liver or renal failure ○ Poor wound healing capacity
Study Assessments	<u>Safety Assessment:</u> • History, physical exam, and routine blood work such as blood counts and comprehensive metabolic panel will be performed on day 1 of each treatment cycle. • Analyses will be performed for all patients having received at least one dose of study drugs. The study will use the NCI CTCAE v4.03. <u>Anti-tumor Assessments:</u> • CT scans of the chest, abdomen, and pelvis and bone scan (when applicable) are to be performed approximately every 8 weeks <u>Exploratory Assessments:</u> • Tumor tissue collection: baseline • Plasma collection: every other month. cfDNA will be performed at baseline , at 4 weeks after treatment initiation (Cycle 2 Day 1), and at disease progression (end-of-treatment) • Pharmacodynamic studies: Day 1 and 15 of cycles 1 and 2 (for escalation portion only) • Pharmacokinetic studies: Day 1 and 15 of cycles 1 and 2 (for escalation portion only)

1. STUDY DESIGN/SUMMARY

This is an open-label, multi-institution, phase Ib trial that evaluates the safety and tolerability and preliminary anti-tumor activity of fulvestrant, palbociclib and erdafitinib in patients with ER+/HER2-/*FGFR*-amplified metastatic breast cancer (MBC). Briefly, patient's eligibility criteria will include: post-menopausal women with metastatic ER+/HER2-/*FGFR*-amplified breast cancer without prior use of a CDK4/6 inhibitor or an FGFR inhibitor; ECOG performance status ≤1, normal baseline blood counts and chemistry laboratory profile; and no intercurrent uncontrolled illness. Treatment will be given until disease progression or unacceptable toxicity. To assess the anti-tumor effect of therapy, we will estimate the overall tumor burden at baseline to which subsequent measurements (performed every 8 weeks using the Solid Tumor Response Criteria [RECIST] v1.1) will be compared. Samples for pharmacokinetic and pharmacodynamic assessments will be obtained throughout the escalation portion of the study. A baseline biopsy of a metastatic site or archival tissue will be obtained in all patients for Next Generation Sequencing, to determine the therapeutic predictive role of *FGFR1-4, CCND1-2, CDK4* and *CDK6* amplifications, and *RB1* and *ESR1* mutations on clinical outcome. Plasma will also be serially obtained, initially for measurement of plasma cell-free tumor DNA (cfDNA) at baseline, at 4 weeks after treatment initiation and at disease progression). This would allow us to determine if the *FGFR1* amplification levels detected by cfDNA at 4 weeks is an early surrogate of response to the triple-combination proposed, and if the cfDNA results at disease progression show new genomic alterations potentially associated with resistance to CDK4/6 and FGFR inhibition.

2. OBJECTIVES AND ENDPOINTS

	Objectives	Endpoints
Primary	To determine the safety and tolerability of fulvestrant, palbociclib and erdafitinib in patients with ER+/HER2-/*FGFR*-amplified MBC	• Assessment of DLT during the first 4 weeks of treatment (cycle 1) • Determination of MTD
Secondary	• To determine the anti-tumor effect of fulvestrant, palbociclib and erdafitinib in patients with ER+/HER2-/*FGFR*-amplified MBC • Pharmacokinetic assessments of erdafitinib	• Progression-free survival (PFS) • Overall response rate (ORR) • Clinical benefit rate (CBR; complete response + partial response + stable disease without disease progression at 6 months) • Pharmacokinetic (PK) assessments of erdafitinib
Correlative	• To determine pharmacodynamic biomarkers of FGFR inhibition • To determine the therapeutic predictive role of *FGFR1-4, CCND1-2, CDK4* and *CDK6* amplifications, and *RB1* and *ESR1* mutations on clinical outcome • To determine if the *FGFR1* amplification levels by FISH and cfDNA is an early surrogate of response • To determine if the cfDNA results at disease progression show new genomic alterations potentially associated with resistance to CDK4/6 and FGFR inhibition.	• Serial measurements of serum phosphate, calcium, vitamin D, parathyroid hormone (PTH), FGF23, sFGFR2, sFGFR3 and sFGFR4 • *FGFR1* FISH • Next Generation Sequencing (NGS) of baseline or archival tumor specimen • Plasma cfDNA at baseline, at 4 weeks and at disease progression

3. BACKGROUND

3.1 Estrogen receptor-positive (ER+) Breast Cancer

Despite advances in early detection and therapeutic options, unresectable or metastatic breast cancer remains incurable and is one of the leading causes of cancer-related mortality[1]. Breast cancer is a molecularly heterogeneous disease with three distinct molecular subtypes[2]. The first group is characterized by estrogen receptor (ER) expression positivity and/or progesterone receptor (PgR) positivity with the absence of over-expression or amplification of HER2. The second group is characterized by over-expression or amplification of HER2, with more than half of these tumors being positive (+) for expression of ER/PgR. The third group lacks detectable ER and PgR, and overexpression of HER2, and is thus referred to as triple-negative breast cancer. Approximately 65% of newly diagnosed breast cancers are ER/PgR+ and HER2-negative (also referred to as luminal tumors), while an additional 20% of newly diagnosed cases are HER2+. ER-targeted drugs, specifically drugs that antagonize estrogen binding to the ER (tamoxifen), drugs that block estrogen biosynthesis (non-steroidal and steroidal aromatase inhibitors [AI] - only effective in postmenopausal patients), and drugs that antagonize and downregulate the ER (fulvestrant), have been the mainstay of systemic treatment for patients with both localized and metastatic ER/PgR+ breast cancers[3].

Fulvestrant is the most recent addition to the armamentarium of hormonal therapies available to treat these patients. However, acquired resistance (and occasionally primary resistance) to anti-estrogen therapy universally develops in patients with ER+ MBC[4]. Interestingly, even after acquired resistance develops, breast cancer cells appear to still depend on low-level ER activity in addition to signaling through sometimes acquired oncogenic signaling pathways[5]. In addition, in patients initially diagnosed with ER/PgR+ localized breast cancer who later recur, tumors usually demonstrate some degree of resistance to antiestrogen therapy at the time of recurrence[6]. Therefore, improving the efficacy of endocrine therapy would be of great benefit to patients with breast cancer and represents a large unmet medical need.

3.1.1 Fulvestrant

Fulvestrant (a selective estrogen receptor downregulator or SERD) is currently a standard of care hormonal therapy option in patients with ER+ MBC[7]. Fulvestrant has an affinity for ER comparable to estradiol. It blocks the trophic actions of estrogens without any partial agonist (estrogen-like) activity, and is currently indicated for the treatment of ER+ MBC in postmenopausal women with disease progression following primary antiestrogen therapy. Clinical trials in postmenopausal women with primary breast cancer have shown that fulvestrant significantly downregulates tumor ER protein levels compared with placebo. There was also a significant decrease in PgR expression consistent with inhibition of ERα transcription. Further, treatment with fulvestrant inhibits tumor cell proliferation as measured by Ki67 immunohistochemistry[8].

Two phase III clinical trials were completed in a total of 851 postmenopausal women with breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease[9]. These trials compared the safety and efficacy of monthly administration of fulvestrant 250 mg vs. the non-steroidal AI anastrozole at 1 mg/daily. Monthly 250 mg fulvestrant was at least as effective as anastrozole in terms of PFS, OR, and time to death. The combined data showed an objective response rate for fulvestrant of 19.2% compared with 16.5% for anastrozole. The median time to death was 27.4 months for patients treated with fulvestrant and 27.6 months for patients treated with anastrozole. The hazard ratio of fulvestrant 250 mg to anastrozole for time to death was 1.01 (95% CI 0.86 to 1.19).

Doses of fulvestrant higher than 250 mg have greater pharmacodynamic activity against the ER pathway. Thus, a 500 mg monthly dose after an initial load is now the FDA-approved standard of care. A phase III clinical trial (CONFIRM)[10] was completed in 736 postmenopausal women with breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease. The study included 423 patients whose disease had recurred or progressed during antiestrogen therapy and 313 patients whose disease had recurred or progressed during AI therapy. This trial compared the efficacy and safety of fulvestrant 500 mg (n=362) vs. 250 mg (n=374). PFS for fulvestrant 500 mg was 6.5 months compared to 5.5 months for fulvestrant 250 mg. Overall survival data from the time of final analysis showed a median time to death of 26.4 months for fulvestrant 500 mg vs. 22.3 months for fulvestrant 250 mg [HR (95%CI) 0.81 (0.69, 0.96), p=0.016].

The routes of elimination for fulvestrant include combinations of a number of possible biotransformation pathways analogous to those of endogenous steroids, including oxidation, aromatic hydroxylation, and conjugation with glucuronic acid and/or sulphate. There are no known drug-drug interactions. Fulvestrant does not significantly inhibit any of the major CYP isoenzymes, including CYP 1A2, 2C9, 2C19, 2D6, and 3A4 *in vitro*, and studies of co-administration of fulvestrant with midazolam indicate that therapeutic doses of fulvestrant have no inhibitory effects on CYP 3A4 or alter blood levels of drugs metabolized by that enzyme. Although fulvestrant is partly metabolized by CYP 3A4, a clinical study with rifampin, an inducer of CYP 3A4, showed no effect on the pharmacokinetics (PK) of fulvestrant. Also results from a healthy volunteer study with ketoconazole, a potent inhibitor of CYP3A4, indicated that ketoconazole had no effect on the PK of fulvestrant, and therefore, dosage adjustment is not necessary in patients with co-prescribed CYP 3A4 inhibitors or inducers.

3.2 Endocrine Therapy and CDK4/6 Inhibition

Identifying well-tolerated targeted therapies that obviate the need for systemic chemotherapy, delay disease progression, and, ideally, prolong survival, as well as characterizing their optimal usage, remain a main objective in breast cancer research. Traditionally, chemotherapy with minimal activity and significant toxicity has been the only option to treat patients with anti-estrogen resistance. This changed in 2012 with the approval of the molecularly targeted mTOR inhibitor everolimus to be used in combination with the steroidal AI exemestane in patients with metastatic ER+/HER2-negative breast cancer who have progressed on a non-steroidal AI. Everolimus appears to at least temporarily restore sensitivity to antiestrogen therapy and results in a PFS benefit[11].

More recently, inhibitors of the cyclin-dependent kinases 4 and 6 (CDK4/6) have demonstrated impressive activity in patients with ER+/HER2-negative MBC with marked improvements in PFS[12].

3.2.1 Palbociclib

Palbociclib is an orally active pyridopyrimidine, first-in-class compound that is a potent and highly selective reversible inhibitor of CDK4/6[13]. Estrogen-activated ER transcription activates cyclin D1 leading to the formation of the cyclin D1-CDK4/6-Rb complex where CDK4/6 phosphorylates and inactivates Rb. Phosphorylated Rb uncouples from E2F transcription factors, which in turn, mediate progression from G1 into S phase of the cell cycle. Thus, by inhibiting CDK4/6, palbociclib prevents tumor cell entry into S phase[14]. Consistent with its CDK4/6 specificity, treatment with palbociclib reduces expression of the proliferation marker Ki67 and is completely inactive in Rb-deficient tumor cells[15]. Preclinical data have shown that endocrine-resistant ER+ breast cancer cells are highly sensitive to the combination of palbociclib with anti-hormonal therapy or palbociclib alone[16].

Blockade of the ER signaling pathway is synergistic with cell cycle arrest induction, as demonstrated by the more than doubling in median PFS observed in the PALOMA-3 clinical trial[17]. The combination of palbociclib with tamoxifen has also shown synergy *in vitro* against ER+ human breast cancer cell lines[18]. Also, recent data in endocrine resistant models (MCF7-CYP19) indicate a significant benefit of the combination of palbociclib and letrozole as well as palbociclib and fulvestrant over letrozole and fulvestrant alone (Pfizer, Investigational Brochure, Version Dec 2013).

Laboratory studies have shown that human breast cancer cell lines that are more sensitive to palbociclib (IC_{50} <150 nM) have low levels of CDKN2A (p16) and high levels of Rb1, while resistant cells show the opposite characteristics. Sensitive cell lines were mostly of the luminal ER+ subtype[16]. A phase I trial tested 3 dose levels of palbociclib in patients with solid tumors, enrolling 41 patients at three dose levels, with drug given for 21 days out of every 28 days[19]. The dose limiting toxicity was neutropenia, and the recommended phase II dose was 125 mg. Clinical benefit with objective response was seen in 10/41 (27%) patients for at least 4 cycles, and in 6 patients for at least 10 cycles, one of whom had breast cancer. Other than neutropenia, which was proportionate to drug exposure, palbociclib was well tolerated.

A phase II study was conducted with single agent palbociclib in 37 women with advanced breast cancer, of whom 89% had ER+ disease[20]. Palbociclib was given at 125 mg orally, days 1- 21 of a 28-day cycle. Over 90% had prior chemotherapy for metastatic disease and 84% had prior endocrine therapy. Clinical benefit was seen in 7 out of the 37 patients, and only in those with ER+ disease for a rate in that subpopulation of 21%. The overall response rate was just 6% in ER+ disease. Grade 3/4 toxicity included neutropenia in 54%, thrombocytopenia in 19%, and grade 1/2 fatigue in 70%.

Encouraging phase II data in patients with ER+/HER2-negative postmenopausal patients with newly diagnosed MBC indicated that the addition of palbociclib to letrozole extends PFS with a tolerable safety profile[17]. The multicenter randomized phase I/II PALOMA-1 study evaluated the combination of palbociclib with the AI letrozole vs. letrozole alone in patients with previously untreated metastatic ER+/HER2-negative MBC[17]. The phase I component of the study established the safety of this combination. The phase II component of the study accrued 165 patients and was divided into two parts, with the first part open to all participants in the study and a second part open only to patients selected for *CCND1* amplification or p16 loss (N=99). After exploratory analysis failed to demonstrate that *CCND1* amplification or p16 loss predicted response to palbociclib, the two parts were combined for a final efficacy analysis. Compared to letrozole alone, the combination of palbociclib and letrozole provided a very impressive increase in PFS, the predefined primary outcome, from 10.2 months to 20.2 months [Hazard Ratio (HR)=0.37; p=0.0004]. Based on these results, in February 2015 the FDA granted accelerated approval for the use of palbociclib and letrozole as first line treatment of patients with ER+/HER2-negative MBC. The confirmatory phase III randomized PALOMA-2 study completed accrual and its preliminary results have been presented at the 2016 American Society of Clinical Oncology (ASCO) meeting[21]. A total of 666 post-menopausal patients with no prior systemic therapy for ER+ MBC were randomized 2:1 to receive letrozole with palbociclib or letrozole with placebo. Median PFS (primary endpoint) was 24.8 months vs. 14.5 months in favor of the palbociclib arm (HR=0.58 [0.46–0.72], p < 0.000001). Response rate was also improved in the palbociclib arm (42.1% vs. 34.7%, p=0.031; 55.3% vs. 44.4% in patients with measurable disease [p=0.013]), and clinical benefit rate was 84.9% vs. 70.3% (p < 0.0001).

The double blind phase III PALOMA-3 trial[22] investigated the combination of fulvestrant and palbociclib in 521 pre- and post-menopausal patients with ER+/HER2-negative MBC, with disease relapse or progression after at least one line of hormonal therapy and at most one line of

chemotherapy, but naïve to CDK4/6 inhibitors[23]. Patients received fulvestrant with placebo or with palbociclib. The PFS at time of interim analysis was 9.2 months in the investigational arm vs. 3.8 months for fulvestrant plus placebo arm (HR=0.42; p<0.000001). The most common grade 3 or 4 adverse events in the palbociclib-fulvestrant group were neutropenia (62.0%, vs. 0.6% in the placebo-fulvestrant group), leukopenia (25.2% vs. 0.6%), anemia (2.6% vs. 1.7%), thrombocytopenia (2.3% vs. 0%), and fatigue (2.0% vs. 1.2%). Thirty-three percent of patients had received one line of prior chemotherapy for metastatic disease. Based on these results, in February 2016 palbociclib was FDA-approved in combination with fulvestrant for second line treatment of patients with ER+/HER2-negative MBC.

Of note, the potential for a clinically significant drug-drug interaction between the CDK4/6 inhibitor palbociclib and fulvestrant is very low. A phase III trial has completed accrual, with an initial safety assessment with trough plasma concentrations demonstrating no pharmacokinetic interactions between fulvestrant and palbociclib[24]. *In vitro* data indicate that CYP3A and SULT enzyme SULT2A1 are mainly involved in the metabolism of palbociclib. The strong CYP3A inhibitor itraconazole increased palbociclib AUCinf by approximately 87%, relative to palbociclib given alone. As expected, coadministration of rifampin, a strong CYP3A inducer, decreased palbociclib AUCinf by 85% relative to palbociclib given alone. Palbociclib is a weak time-dependent inhibitor of CYP3A following administration of the clinical 125 mg dose: palbociclib increased the midazolam AUCinf values by 61%, as compared with midazolam alone. *In vitro*, palbociclib is not an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, and 2D6, and is not an inducer of CYP1A2, 2B6, 2C8, and 3A4 at clinically relevant concentrations. In vitro evaluations indicated that palbociclib has a low potential to inhibit the activities of drug transporters at clinically relevant concentrations.

3.3 Fibroblast Growth Factor Receptor-1 (FGFR1) in ER+ Breast Cancer

Somatic mutations in the FGFR pathway result in its aberrant activation, leading to cellular transformation, tumorigenesis and cancer progression[25]. Several lines of evidence support a role for FGFRs in breast cancer[26]. *FGFR1* amplification is present in about 15% of ER+ breast cancers[27], and is an independent predictor of overall survival in patients with ER+ breast cancer treated with tamoxifen[28]. *FGFR* overexpression has been shown experimentally to mediate resistance to endocrine therapy through activation of the MAPK and PI3K pathways[26]. About 30-40% of breast tumors with *FGFR1* amplification also exhibit amplification of *CCND1*, *FGF3/4/19* in chromosome 11q[29]. This co-amplification is also associated with a reduction of patients' survival[30]. Based on these data, several pharmaceutical companies have developed drugs targeting FGFR (**Table 1**), focusing their

Table 1. FGFR inhibitors

	JNJ-42756493 IC_{50} (nM)	BGJ398 IC_{50} (nM)	AZD4547 IC_{50} (nM)	Lucitanib IC_{50} (nM)
FGFR1	< 1	4.55	< 1	21
FGFR2	< 1	28.1	< 1	41
FGFR3	1.05	19.5	2.52	51
FGFR4	< 1	376	40.6	----------
FGFR3 (G697C)	1.90	28.8	5.25	----------
VEGFR1	----------	----------	----------	1
VEGFR2	----------	----------	----------	1.1
VEGFR3	----------	----------	----------	7.1
PDGFRα	----------	----------	----------	0.43
PDGFRβ	----------	----------	----------	0.26

clinical development on tumor subtypes with a high likelihood of dependence on FGFR pathway signaling. These include tumor types with *FGFR* amplifications, activating mutations and fusions.

3.3.1 Erdafitinib

Erdafitinib (JNJ-42756493), a potent, oral pan-FGFR tyrosine kinase inhibitor with IC_{50} values in the low nanomolar range for FGFR 1-4, was recently tested in a phase I trial in solid tumors[31]. It has demonstrated potent inhibition of cell proliferation with IC_{50} values ranging from <1 to <1000 nM in FGFR pathway-activated cancer cell lines including squamous non-small cell lung cancer (NSCLC), gastric, breast, hepatocellular cancer (HCC), endometrial, bladder, multiple myeloma, and acute myeloid leukemia. Non-FGFR driven cell lines require significantly higher drug concentration for inhibition of cell proliferation to be observed. Target inhibition and pathway modulation have been demonstrated in cellular models at the active cellular concentrations. Brief exposure (1 h) to erdafitinib has been demonstrated to result in long-term (>8 h) target inhibition. Erdafitinib inhibits the growth of pre-established subcutaneous (s.c.) and orthotopically injected xenografts tumors in both immunodeficient mice and rats. Tumor regression was observed in rats bearing human *FGFR2*-overexpressing SNU-16 gastric cancer xenografts after oral administration at 20 and 50 mg/kg daily doses of JNJ-42756493. Similar findings were observed in mice with SNU-16 tumors and patient-derived gastric, breast, hepatocellular, and NSCLC xenografts.

Erdafitinib exhibited a dose-related increase in Cmax and area under the analyte concentration-time curve (AUC) and time-independent PK within the dose range of 0.5 to 12 mg, both after single and multiple daily dosing. The actual sampling time to reach maximum concentration (tmax) ranged between 2-4 hours (erdafitinib as tablet), independent of the studied formulations. PK was characterized by moderate intersubject variability (CV% 31-39%) and low intra-subject variability (9-10%). Erdafitinib is primarily excreted in feces either as unchanged drug or as metabolites. In vitro data indicated that CYP3A and 2C9 are involved in erdafitinib metabolism. 70% and 20% of the radioactivity was recovered in feces and urine, respectively, with approximately 11% of unchanged drug recovered in urine. Erdafitinib is highly bound to plasma proteins, especially to α1-AGP (fraction unbound in oplsma being 0.36% and 0.50% in patients and healthy subjects, respectively. Apparent volume of distribution (Vd/F) of the terminal phase based on total plasma erdafitinib in healthy subjects is small (approximately 31 L), suggesting it is limited by the binding to plasma protein. Erdafitinib has low total plasma oral clearance (mean CL/F in subjects with cancer averaged 0.29 L/h; the corresponding value for healthy subjects was 0.43 L/h), likely restricted by protein binding. As a consequence, the apparent elimination half-life (t1/2) of erdafitinib is long (approximately 50 hours in healthy subjects) resulting an approximately 3- to 4-fold accumulation in Cmax and AUC following multiple daily dosing.

Erdafitinib is being investigated as an anti-cancer agent in several clinical studies (refer to most updated version of erdafitinib IB). As of June 2016, 305 subjects have been treated with erdafitinib. The median extent of drug exposure as of June 2016 was 7 weeks (range: 0 – 102 weeks). There does not appear to be any dose-related trends in mean or median drug exposure, suggestive of tolerability of the drug. As for clinical efficacy, responses were observed at doses of 9 mg once daily or higher (range of responses: ~12 – 40%), particularly in patients with FGFR mutations.

The most common adverse events included hyperphosphatemia (63%), asthenia (55%), dry mouth (45%), skin toxicities (38%), nail toxicity (30%), constipation (34%), decreased appetite (32%), and dysgeusia (31%), and eye toxicities (25%)[31]. Of note, QT prolongation was not reported. Adverse events of special interest include events that are class effects of FGFR inhibitors that have been experienced by patients treated with other FGFR inhibitors. These events include skin (xerosis, skin fissures, palmar-plantar erythrodysesthesia), mucosal (dryness,

mucositis, ulceration), nail changes (onycholysis, nail dystrophy), hyperphosphatemia, and eye toxicities (dry eyes, keratitis, and reversible retinal pigment epithelial detachment - RPED or central serous retinopathy [CSR]).

3.4 FGFR and CDK4/6 Inhibition in ER+ Breast Cancer - Preliminary Data

A. In a pre-surgical study with the aromatase inhibitor letrozole in post-menopausal patients with ER+/HER2-negative operable breast cancer (NCT00651976), we discovered that amplification of *FGFR1* (in 8p) and *CCND1*, *FGF3/4/19* (in 11q), previously associated with tamoxifen resistance[28], was statistically more frequent in tumors that retain high proliferation, as measured by Ki67 immunohistochemistry (IHC), upon treatment. FGFR1 IHC of primary tumors showed an increase in FGFR1 expression in tumor cell cytoplasm and nucleus after treatment with letrozole only in *FGFR1*-amplified cancers, suggesting that *FGFR1* amplification is a mechanism of resistance to letrozole-induced estrogen deprivation. We performed Proximity Ligation Assays (PLA) and confocal microscopy in sections from primary tumors and found an increase in a nuclear ERα/FGFR1 complex following letrozole treatment. Chromatin immunoprecipitation (ChIP) with FGFR or ERα antibodies of crosslinked DNA-proteins from estrogen-deprived ER+/*FGFR1* amplified cells showed recovery of PCR amplified gene promoters containing estrogen-response elements (EREs), suggesting an estrogen-independent FGFR1-ERα interaction driving ER transcription and potentially explaining the antiestrogen resistance seen in *FGFR*-amplified tumors treated in the trial. The observed FGFR1-ERα association was abrogated by treatment of cells with the FGFR TKI lucitanib or by transfection of a tyrosine kinase dead (K514M) mutant of FGFR1, suggesting it is dependent on the FGFR1 tyrosine kinase activity. Finally, co-treatment of ER+/*FGFR1*-amplified CAMA-1 breast cancer cells with lucitanib and fulvestrant was markedly more effective than either lucitanib or fulvestrant alone, while simultaneously inhibiting p-FRS2 and p-ERK and downregulating ER levels (**Figure 1**).

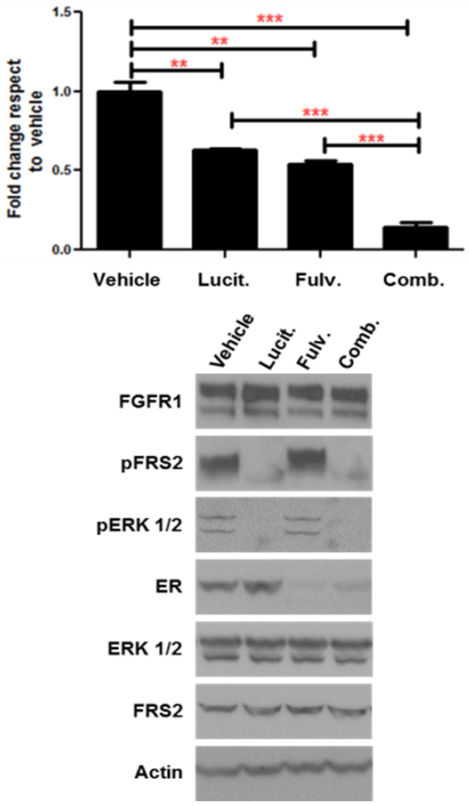


Figure 1. ER+/FGFR1 amplified CAMA-1 human breast cancer cells were plated in 3D-Matrigel in presence of FGF3 (100 ng/ml) ± vehicle, lucitanib, fulvestrant or both drugs combined. Media was replenished every three days. After 14 days, the plates were stained with crystal violet and read by Gel Count. Fold change relative to vehicle treated monolayers is shown as bar graphs (**p<0.01***p <0.001, t-test). CAMA-1 cells from identically treated parallel plates were treated for 6 h. Cell lysates were then prepared and subject to immunoblot analyses with the indicated antibodies. Only the combined therapy simultaneously reduced levels of ERα, P-FRS2 and P-ERK.

B. To identify potential mechanisms of resistance to fulvestrant alone and in combination with a CDK4/6 inhibitor, we conducted a gain-of-function discovery screen using a library containing 559 human kinases open reading frames (ORFs)[32] in MCF7 ER+ breast cancer cells treated with fulvestrant ± LEE011 (ribociclib, Novartis), a small molecule CDK4/6 inhibitor with an IC_{50} against CDK4 and CDK6 of 10 and 39 nM, respectively. In both screens, FGFR1 was the top ORF rescuing from the antitumor effect of fulvestrant ± ribociclib. This result was confirmed in a secondary screen using fulvestrant ± the FDA-approved CDK4/6 inhibitor palbociclib.

ER+/*FGFR1*-amplified CAMA-1, MDA-134 and HCC1500 breast cancer cells were relatively resistant to the combination of fulvestrant and palbociclib compared to ER+/FGFR-low MCF7 cells. In CAMA-1 cells, addition of lucitanib to fulvestrant and palbociclib completely eliminated CAMA-1 cell viability. Consistent with the potent growth inhibition observed, the triple therapy was most effective at simultaneously reducing p-Rb, ERα and p-ERK levels after only 6 h of treatment (**Figure 2**).

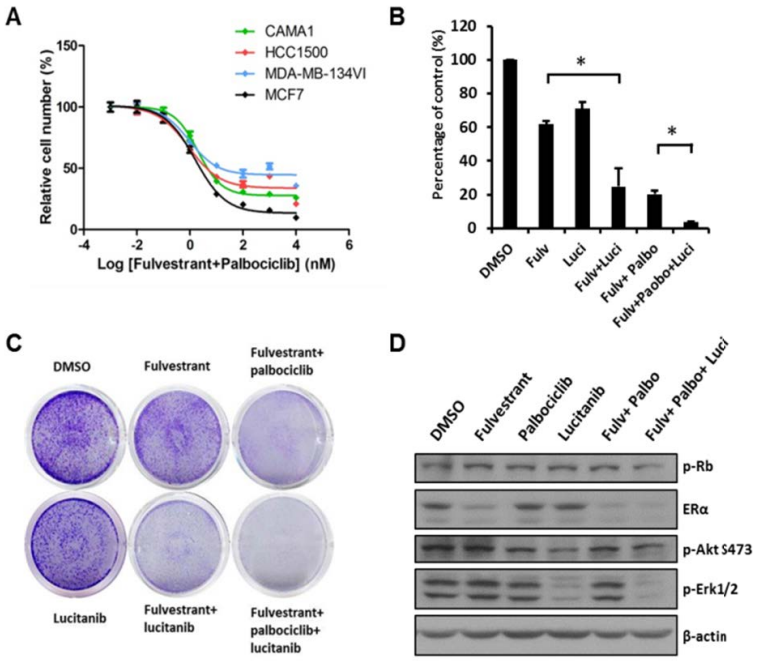


Figure 2. A) 1x10^4 ER+/FGFR1 amplified (CAMA1, HCC1500 and MDA-MB-134) and ER+/FGFR1 non-amplified (MCF7) breast cancer cell lines were plates in 384-well plated in presence of fulvestrant and palbociclib over a dose range. After 6 days, cells were harvested and cell numbers measured in a Coulter counter. **B-C**) CAMA1 cells (≈5x10^4/well) were seeded in 6-well plates in triplicate in full media in presence of FGF2 (1 ng/ml) and treated with vehicle or the indicated inhibitors alone or in combination for 15 days. Media and inhibitors were replenished every three days. After 14 days, cell monolayers were fixed and stained with crystal violet. Each bar represents the mean integrated intensity ± SE of triplicate wells relative to DMSO treated controls (*p<0.05, t-test). The triple combination of fulvestrant, palbociclib and lucitanib completely eliminated tumor cell growth. **D)** CAMA1 cell lines treated vehicle or the indicated inhibitors alone or in combination for 6 hours. The triple therapy was most effective at rapidly downregulating levels of P-Rb, ERa and P-ERK.

Finally, in nude mice bearing either MCF7-wild type cells (MCF7^{wt}) transduced with a lentivirus control vector or MCF7 cells overexpressing a stably transduced FGFR1 expression vector (MCF7^{FGFR1}) xenografts, the combination of lucitanib, fulvestrant and palbociclib was markedly more effective in reducing or eliminating established tumors than either lucitanib alone or the combination of fulvestrant and palbociclib. This difference was particularly strong in mice with MCF7^{FGFR1} xenografts (**Figure 3**).

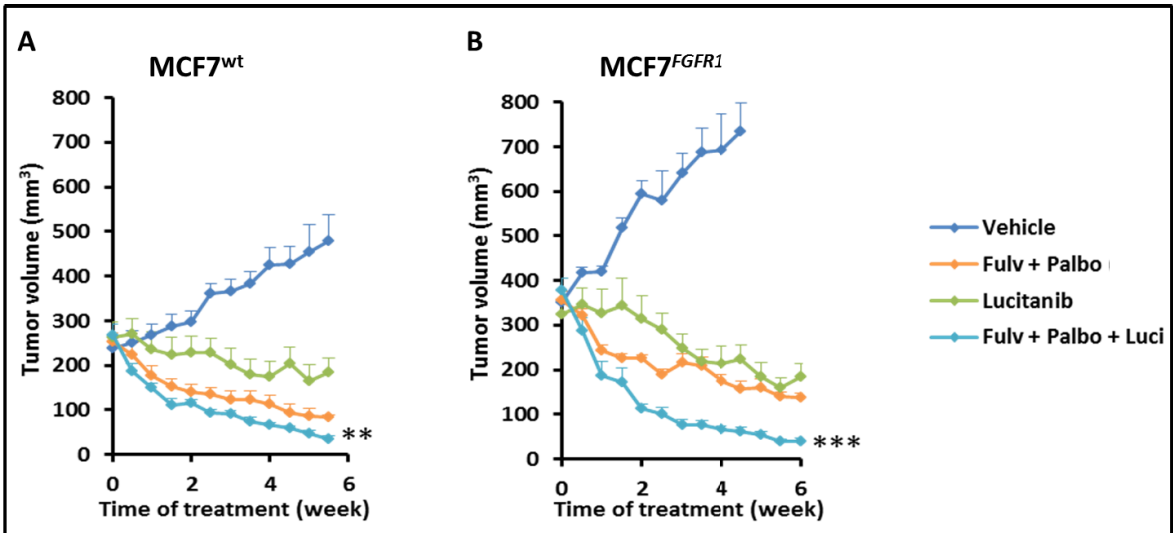


Figure 3. MCF7-wildtype (MCF7^{wt}) cells (**A**) and MCF7-FGFR1 overexpressed (MCF7^{FGFR1}) cells (**B**) were injected s.c. in the dorsum of female athymic mice supplemented with a 14-day release, 0.17 mg 17b-estradiol pellet. Mice bearing tumors ≥ 250 mm^3 were randomized to vehicle, lucitanib (10 mg/kg/day p.o.), fulvestrant (5 mg/week s.c.) plus palbociclib (30 mg/kg/day p.o.), or the combination of fulvestrant, palbociclib and lucitanib for 6 weeks (n=9 per treatment arm). Tumors were serially measured with calipers and tumor volume in mm^3 calculated by the formula: volume = width^2 x length/2. Each data point represents mean tumor volume in mm^3 ± SEM (** p<0.01; *** p<0.001 vs. fulvestrant plus palbociclib by t-test). Mice maintained body weight during whole treatment period with no deaths observed.

Similarly, in an ER+/*FGFR1*-amplified TM00368 patient-derived xenograft (PDX) model the combination of fulvestrant, palbociclib and erdafitinib was also markedly more effective in reducing or eliminating established tumors than either palbociclib or fulvestrant alone or the combination of fulvestrant and palbociclib (**Figure 4**).

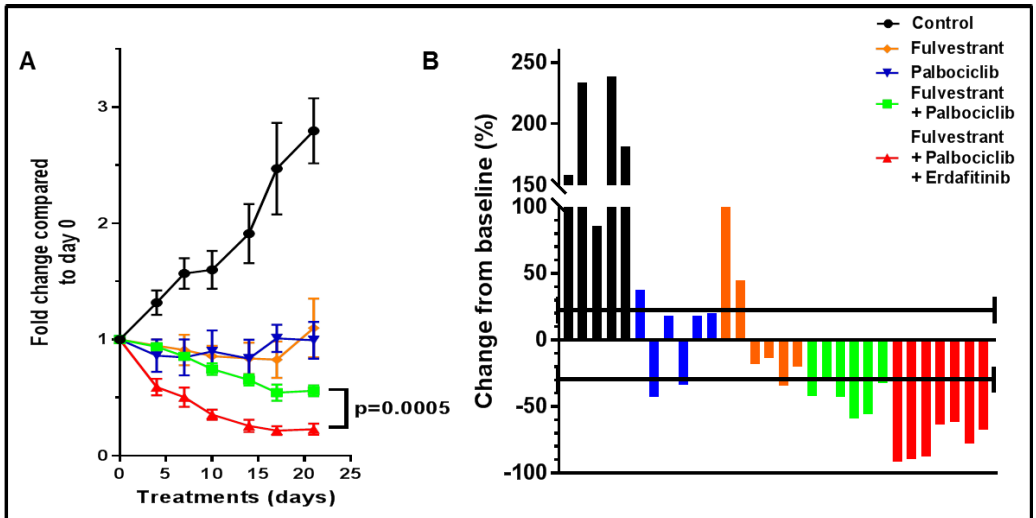


Figure 4. A, ER+/HER2–/*FGFR1*-amplified TM00368 PDX fragments were established in ovariectomized SCID/beige mice implanted s.c. with a 21-day release, 0.25-mg 17b-estradiol pellet. Once tumors reached ≥200 mm^3, mice were randomized to treatment for 3 weeks with vehicle (control), fulvestrant (5 mg per week), fulvestrant + palbociclib (30 mg/kg/day) or fulvestrant plus palbociclib plus erdafitinib (12.5 mg/kg/day). Each data point represents the fold change in volume ± SEM (n=8 per arm; ANOVA test). **B,** Bar graph showing the % change in volume in individual TM00368 PDXs after three weeks of treatment relative to tumor volumes on day 0 (baseline).

3.5 Rationale

Preliminary evidence demonstrates that specific FGFR blockade with compounds such as erdafitinib has a manageable tolerability profile with promising clinical activity. The optimal strategies for combining FGFR inhibition with other anticancer agents requires further research. Ongoing clinical trials with FGFR inhibitors are being enriched for tumors harboring specific *FGFR* mutations and amplifications presumed to be highly addicted to this pathway. To date, preliminary clinical data suggest that FGFR and/or FGF3/4/19 ligand amplification is associated with clinical benefit from FGFR inhibitors[33,34], suggesting these are biomarkers of tumor dependence on the FGF/FGFR pathway. Other data in support of this hypothesis are:

- In ER+ breast cancers, most *FGFR1* amplifications coexist with 11q amplification (*CCND1, FGF3/4/19*) and are associated with endocrine resistance[30]
- Activation of FGFR1 increases transcription and expression of cyclin D1 (not shown)
- In ER+/*FGFR1*-amplified breast cancer cells, an FGFR inhibitor does not inhibit pRb and a CDK4/6 inhibitor does not inhibit ERK or AKT (**Figure 2**)
- The combination of FGFR and CDK4 inhibitors has a synergistic effect against *FGFR1*-amplified breast cancer cells (**Figure 3 and 4**)

We hypothesize that *FGFR* amplification attenuates the response of ER+ breast cancers to the combination of ER and CDK4/6 antagonists. Thus, the triple combination of an antiestrogen plus a CDK4/6 and an FGFR inhibitor would have synergistic activity in ER+/*FGFR*-amplified MBC. In this application, we propose a clinical trial of fulvestrant, palbociclib with the FGFR tyrosine kinase inhibitor (TKI) erdafitinib in patients with ER+/ HER2–/*FGFR1-4*-amplified MBC. Within this proposal, we will perform a dose escalation phase Ib study to determine the safety and tolerability and preliminary anti-tumoral activity of the triple combination. Once the recommended dose for phase II trials (RDP2) is defined, a future open-label randomized phase II trial of fulvestrant and palbociclib with or without erdafitinib will be conducted.

3.6 Correlative Science Background

3.6.1 Blood Samples for Pharmacodynamic Assessments

As previously shown[31,35], FGFR inhibition is expected to produce blockade of FGF23 release from the bone and, therefore, hyperphosphatemia and changes on vitamin D and PTH are considered on-target effects. Blood collection for pharmacodynamic assessments (serum phosphate, calcium, vitamin D, parathyroid hormone [PTH], FGF23, sFGFR2, sFGFR3 and sFGFR4) will be performed on Days 1 (pre-treatment) and 15 of Cycle 1 and 2 in all patients participating in the phase Ib escalation portion of the study, to confirm drug target engagement by erdafitinib.

3.6.2 Blood Samples for cfDNA

Circulating DNA fragments carrying tumor-specific sequence alterations (circulating tumor DNA) are found in the cell-free fraction of plasma, representing a variable and generally small fraction of the total circulating DNA[36,37]. Circulating tumor DNA is an informative, inherently specific, and highly sensitive biomarker of metastatic breast cancer, as it has shown good correlation with changes in tumor burden and early tumor response[38]. Therefore, to determine if the level of *FGFR1* amplification in plasma is an early surrogate of response, and to determine if the cfDNA results at disease progression show new genomic alterations associated with resistance to CDK4/6 and FGFR inhibition, blood collection for cfDNA will be performed every other month in all patients, but cfDNA analysis, initially, will be performed at the following time-points: baseline (Cycle 1 Day 1), at 4 weeks after treatment initiation (Cycle 2 Day 1), and at disease progression (end-of-treatment).

3.6.3 *FGFR1* Fluorescence *In Situ* Hybridization (FISH)

In situ hybridization scoring techniques for characterizing *FGFR1-2* amplification have varied in trials reported to date[39]. Although amplification of FGF3/4/19 ligands may also predict those patients more likely to benefit from FGFR blockade[33], the heterogeneity in published definitions makes it difficult to assess the true significance of these biomarkers given the lack of standardized measurement. Nevertheless, it is a reproducible test that can be done in a CLIA certified laboratory and has a quick turn-around. We propose to utilize *FGFR1* FISH analysis in all patients enrolled in this study as a screening method for eligibility, and to determine the therapeutic predictive role of *FGFR1* amplification by FISH on FFPE blocks on clinical outcome.

In view of the higher prevalence of *FGFR1* amplification compared to *FGFR2-4* amplifications, patients with known *FGFR1* amplification (by targeted capture next gene sequencing, cfDNA or FISH) will require central confirmation of *FGFR* amplification by FISH, but will not be required to wait for that result to initiate study treatment. Patients without known *FGFR1* amplification will be screened by FISH analysis at the Vanderbilt-Ingram Cancer Center (VICC). From the time tissue arrives at the Coordinating Center Breast Cancer Tissue Core (Dr. Melinda Sanders), a turn-around time of no longer than 7 days should be expected for the FISH results to become available.

Tumors are considered as *FGFR1* positive ('amplified') under one of the following conditions:

(1) The *FGFR1*/CEN8 ratio is ≥2.0;
(2) The average number of *FGFR1* signals per tumor cell nucleus is ≥6[40].

3.6.4 Targeted capture next generation sequencing (NGS)

- Amplification of *FGF3/4/19* ligand genes on chromosome 11q12-14 has been observed in 15% of human breast cancers[41,42]. Notably, one-third of *FGFR1*-amplified tumors also harbor amplification of *CCND1, FGF3, FGF4* and *FGF19*[30]. This co-amplification has been associated with resistance to estrogen deprivation in ER+ breast cancer and poor patient outcome[30], thus suggesting the possibility of ligand-receptor cooperativity.
- Recent studies suggest that acquired resistance to CDK4/6 inhibition in ER+ breast cancer results from bypass of cyclin D1–CDK4/6 dependence as a result of *CCNE1* amplification or *RB1* loss[43].
- *ESR1* mutations, which occur in ~25% of metastatic breast cancer progressing on aromatase inhibitors, are an emerging mechanism of endocrine resistance[44,45]. The combination of fulvestrant and palbociclib has been shown to be effective against *ESR1*-mutant cell line-derived and patient-derived xenografts[18]. This combination was also effective among patients harboring *ESR1* mutant cancers in the PALOMA-3 trial[22]. Our preliminary data in **Figure 2** would suggest aberrant FGFR signaling limits the effect of fulvestrant/palbociclib and, therefore, in these patients the addition of an FGFR inhibitor may be beneficial.

Therefore, we will determine the therapeutic predictive role of *FGFR1-4, FGF3/4/19, CCND1-2, CDK4* and *CDK6* amplifications, and *RB1* and *ESR1* mutations on clinical outcome, FFPE tissue from primary tumor or from a metastatic tumor biopsy will be collected for NGS in all patients enrolled in the study at the time of registration.

4. PARTICIPANT SELECTION

4.1 Inclusion Criteria

4.1.1 Patients (female or male) must provide informed written consent and must complete all screening assessments as outlined in the protocol

4.1.2 Patients must be able to swallow and retain oral medication

4.1.3 Patients must be ≥ 18 years of age

4.1.4 Female patients of no childbearing potential.

Patient must be post-menopausal by at least one of the following criteria prior to enrollment:

a. Subjects at least 60 years of age; OR

b. Subjects under 60 years of age and naturally (spontaneous, no alternative pathologic or physiological cause) amenorrhea for at least 12 months; OR

c. Medical ovarian failure confirmed by follicle-stimulating hormone (FSH) and estradiol levels in the post menopausal range per local institutional normal range; OR

d. Prior bilateral oophorectomy; OR

e. Prior radiation castration with amenorrhea for at least 6 months; OR

f. Treatment with a luteinizing hormone-releasing hormone (LH-RH) agonist (such as goserelin acetate or leuprolide acetate) is permitted for induction of ovarian suppression as long as it has been initiated at least 28 days prior to study enrollment

4.1.5 ECOG performance status 0 - 1

4.1.6 Clinical stage IV or inoperable locoregional recurrent invasive mammary carcinoma that is:

a. ER+ and/or PgR+ (≥ 1% positive stained cells) by immunohistochemistry (IHC)

b. HER2-negative (by IHC or FISH, per ASCO guidelines)

c. *FGFR1 – 4* amplified* (may be determined by local assessment through either targeted capture next generation sequencing (NGS), plasma cell-free tumor [cf] DNA or FISH [in the case of *FGFR1* amplifications]*) in 50% of the patients participating in the expansion cohort of the trial (not necessary in the escalation cohort)

**Cases will be considered as FGFR1-positive ('amplified') under one of the following conditions:*

(1) The FGFR1/CEN8 ratio is ≥2.0;
(2) The average number of FGFR1 signals per tumor cell nucleus is ≥ 6[40]

d. Evaluable (may have either measurable or non-measurable disease)

4.1.7 Patients must have available tissue [archived formalin-fixed paraffin embedded (FFPE) blocks or fresh frozen biopsy from primary tumor or metastatic tumor biopsy] for correlative studies. Tissue source needs to be located and available at the time of registration (tissue needs to be submitted within 3 weeks of study initiation). Patients will not be able to start study drugs without tissue availability. Submission of tissue can be waived, if approved by the Study Chair in case of extraordinary/ catastrophic circumstances

4.1.8 Patients must have had at least one line of systemic therapy in the metastatic setting

4.1.9 Current use of any of the drugs listed on the Cautionary Concomitant Med list has to be approved by the Study Chair

4.1.10 Patients must have adequate hematologic, hepatic and renal function. All laboratory tests must be obtained within 2 weeks from study drug initiation. These include:

a. ANC ≥ 1,500/mm^3
b. Platelet count ≥ 100,000/mm^3
c. HgB ≥ 9.0 g/dL
d. Creatinine clearance ≥ 40 mL/min/1.73 m^2
e. SGOT, SGPT ≤ 2.5 x ULN if no liver metastasis present; SGOT, SGPT ≤ 4 x ULN if liver metastasis present
f. Albumin ≥ 2.0 g/dL
g. Total serum bilirubin ≤ 1.5 x ULN (≤ 3 x ULN or direct bilirubin ≤ 1.5 x ULN if known Gilbert's syndrome)
h. Potassium within institutional normal limits
i. Phosphorus ≤ institutional upper limit of normal

4.2 Exclusion Criteria

4.2.1 Prior use of an FGFR inhibitor

4.2.2 More than 2 lines of chemotherapy in the metastatic setting. No limit on endocrine therapy lines. Prior exposure to CDK4/6 inhibitor acceptable.

4.2.3 Radiation therapy ⩽ 2 weeks prior to study entry. Patients who have received prior radiotherapy must have recovered from toxicity (≤ grade 1) induced by this treatment (except for alopecia)

4.2.4 Prior cancer therapy (except for endocrine therapy) must have been discontinued for 1 week prior to initiation of study drugs

4.2.5 Concurrent anti-cancer therapy other than the ones specified in the protocol is not permitted during study participation. Bisphosphonates or denosumab are allowed

4.2.6 Major surgery within 4 weeks of enrollment

4.2.7 Herbal preparations are not allowed throughout the study, and should be discontinued 14 days prior to initiation of study treatment

4.2.8 Any corneal or retinal abnormality likely to increase the risk of eye toxicity, such as:

a. Current corneal pathology such as keratitis, keratoconjunctivitis, keratopathy, corneal abrasion, inflammation or ulceration

b. Uncontrolled glaucoma despite standard of care therapy

c. Diabetic retinopathy with macular edema

d. Known active wet, age-related macular degeneration (AMD)

e. Known central serous retinopathy (CSR) or retinal vascular occlusion (RVO)

4.2.9 Uncontrolled intercurrent illness including, but not limited to:

a. Malabsorption syndrome significantly affecting gastrointestinal function

b. Ongoing or active infection requiring antibiotics/ antivirals

c. Impairment of lung function (COPD > grade 2, lung conditions requiring oxygen therapy)

d. Symptomatic congestive heart failure (class III or IV of the New York Heart Association classification for heart disease)

e. Unstable angina pectoris, angioplasty, stenting, or myocardial infarction within 6 months

f. Clinically significant cardiac arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia that is symptomatic or requires treatment [National Cancer Institute -Common Terminology Criteria for Adverse Events, Version 4.03, grade 3]

g. QTcF ≥ 480 msec on screening EKG

h. Known history of clinically significant QT/QTc prolongation or Torsades de Pointes (TdP)

i. ST depression or elevation of ≥ 1.5 mm in 2 or more leads

j. Diarrhea of any cause ≥ CTCAE grade 2 that does not resolve within a few days when adequately treated with anti-diarrhea medications

k. Psychiatric illness/social situations that would compromise patient safety or limit compliance with study requirements including maintenance of a compliance/pill diary

l. Symptomatic brain metastases (patients with a history of brain metastases must be clinically stable for more than 4 weeks from completion of radiation treatment and be off steroids)

m. Known history of chronic liver or chronic renal failure

n. Poor wound healing capacity

4.3 Inclusion of Underrepresented Populations

Individuals of all races and ethnic groups are eligible for this trial. There is no bias towards age or race in the clinical trial outlined. This trial is open to the accrual of women and men.

5. REGISTRATION PROCEDURES

5.1 Guidelines for VICC and TBCRC Institutions

Prior to registration, a copy of the IRB approval at the site will be requested and on file at VICC. Eligible participants will be entered on study centrally at the VICC Coordinating Center by the Project Manager or designee. All sites should email the Project Manager or designee at **coordinating.center@vumc.org** to verify treatment availability.

All patients MUST be registered with the Vanderbilt-Ingram Cancer Center (VICC) prior to the start of protocol treatment. Registration can only be conducted during the business hours of 8AM – 5PM Monday through Friday.

Note: VICC Coordinating Center requests 24-48 hours to review all documents and confirm eligibility. Same day treatment registrations will only be accepted with prior notice and discussion with the Lead Institution. Please email the CTO if enrollment is needed sooner at coordinating.center@vumc.org.

The registration procedures are as follows:

1) All sites should email the Coordinating Center at coordinating.center@vumc.org: to notify of upcoming registration and slot availability.
2) Copy of the patient's signed and dated Informed Consent including documentation of the consent process
3) Patient Enrollment Form
4) Complete provided protocol-specific eligibility checklist (using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criterion listed in the eligibility checklist.**
5) Tissue Block Registration
6) Email the following documents to the Coordinating Center **coordinating.center@vvumc.org**:
    - Completed Eligibility Checklist
    - Copies of laboratory, imaging and pathology reports
    - Patient signed complete Consent Form
    - HIPAA authorization form (if separate from the main consent form)
    - Tissue Block Registration
    - Copy of the IRB approval at the site (if not previously sent)
7) Once registration confirmation from Coordinating Center is received, proceed with protocol procedures.

Please contact the Clinical Research Specialist or designee at **coordinating.center@vumc.org** with any questions regarding this process.

The VICC Coordinating Center will assign sequence numbers to all patients in screening. Only patients deemed eligible will be registered to investigational treatment. Sequence numbers will not be re-used if a patient screen fails. Following registration, eligible participants should begin

study treatment consistent with the protocol no later than 28 days after registration by the VICC Coordinating Center. If a participant does not receive protocol therapy following registration within the allowed time period, the participant's registration on the study may be canceled. The Project Manager should be notified of cancellations as soon as possible.

Issues that would cause treatment delays should be discussed with the Protocol Chair. If a participant does not receive protocol therapy following enrollment within allowed time period, the participant will become ineligible and will be removed from the study. Such patients will have to undergo re-screening in order to participate in the study. Any requests for eligibility exceptions and/or deviations must be approved in writing by the Protocol Chair, the VICC DSMC and the IRB.

As is generally accepted, standard of care procedures performed prior to consent, but within the protocol defined screening window for each assessment, can be used for study purposes. All research-only procedures must be performed after the consent date.

6. STUDY CALENDAR

Parameter	Pre-Study[1]	Month/Week/Cycle				End of Treatment[6]	28 Day Follow-up[17]	Long Term Follow-up[18]
		D1, 8, 15 and 22 Cycle 1	D1 and 15 Cycle2	D1 of every Cycle[9]	Every 8 weeks			
Demographics	X							
CLINICAL EVALUATIONS:								
History and Physical	X	X	X	X		X		
Toxicity Assessments	X	X	X	X		X	X	
Concomitant Medications Assessments	X	X	X	X		X		
Height	X							
Vital Signs and Weight	X	X	X	X		X		
Performance Status	X	X	X	X		X		
Ophthalmologic Exam	X[12, 13, 14]							
Amsler Grid Test[12, 14]				X		X		
LABORATORY/RADIOLOGIC EVALUATIONS:								
Hematology (CBC/diff, PLT)	X	X	X	X		X		
Comprehensive Metabolic Panel[2]	X	X	X	X		X		
Magnesium	X	X	X	X		X		
Phosphorus	X	X	X	X		X		
Parathyroid Hormone (PTH)		X[8]	X					
Total vitamin D		X[8]	X					
EKG	X							
Tumor Evaluation[3]	X				X			
TREATMENT ADMINISTRATION:								
Erdafitinib		Daily						
Palbociclib		Days 1 - 21 of every 28-days cycle						
Fulvestrant		X[10]		X				
Pill Diary[5]				X				

Meal Record		X[16]	X					
CORRELATIVE STUDIES:								
Tumor Tissue Collection[4]	X							
Blood Collection needed to accompany tissue for NGS analysis[15]	X							
FGFR1 FISH Analysis	X							
Blood Collection for cfDNA[11]	X				X	X		
Blood Collection for Pharmacokinetic Assessments		X[7]	X					
Blood Collection for Pharmacodynamic Assessments		X[8]	X					
FOLLOW-UP:								
Chart review for progression status[18]								X

Notes:

- Additional tests may be performed at the discretion of the treating investigator as clinically indicated. The sample collection schedules outlined above are based on an ideal subject.
- **All appointment/procedures may be performed ± 3 days to accommodate unexpected scheduling issues, weekends and holidays.** The sample schedule should be followed as closely as is realistically possible; however, the schedule may be modified due to problems such as scheduling delays or conflicts (e.g., clinic closure, poor weather conditions, vacations, etc.).
- Shaded cells (gray) represent **RESEARCH** procedures; white cells represent **STANDARD OF CARE** procedures

1. Pre-study assessments should be performed within 28 days prior to starting treatment, unless otherwise noted. Please note that the labs obtained on Cycle 1, Day 1 also need to meet eligibility criteria. Screening procedures (i.e. history and physical exam, etc.), excluding labs, which are conducted within 1 week of C1D1 do not need to be repeated. Labs performed on C1D1 for screening are permitted given that they are submitted to the Coordinating Center and approved prior to study treatment initiation.
2. Chemistry includes measurement of sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total bilirubin, calcium, total protein, albumin, AST, ALT, and alkaline phosphatase.
3. CT scans (chest/abdomen/pelvis) are acceptable for tumor evaluations. MRI of the brain is to be performed only at the discretion of treating physician. Baseline scans should be performed up to 4 weeks prior to study drugs initiation. The scans may be performed ± 5 days of patient's scheduled appointment, to accommodate weekends and holidays
4. FFPE blocks may be from the primary tumor (time of original diagnosis) or a metastatic biopsy site. If available, a previously stored fresh-frozen tissue will also be collected. Tissue collected should be submitted at the time of registration. If patients are agreeable, at any time prior, during, or after study drug exposure, an optional (but encouraged) fresh-frozen tissue research biopsy of a metastatic site of disease will be performed and collected (see Section 10.3 for more details). It is assumed that about 20% patients will agree to a fresh biopsy.
5. Pill Diary dispensed with study drug for all patients in the study.

6. End of treatment procedures will be carried out after patients are off study drugs at either their current visit or within 7 days of coming off the study drug.
7. Blood for PK (see Section 10): Plasma for pharmacokinetic assessments will be collected on **Days 1** and **15** of **Cycles 1** and **2** only in patients participating in the escalation portion of the trial. Of note, PK samples could be obtained from additional patients if there are concerns about the PK profiling and/or clinical safety based on the available results. For further details (including sampling schedule if an alternative dosing schedule is adopted) please see the **Lab Manual**. A meal record should be completed on days of PK assessment.
8. Blood for pharmacodynamic assessments [serum Calcium, Phosphate, PTH, vit D, FGF23, sFGFR2, sFGFR3 and sFGFR4; Section 10] will be performed on **Days 1** and **15** of **Cycles 1** and **2** in all patients in the escalation part of the trial.
9. C1D1 procedures are not required; the baseline procedure will be the one done within 28 days of trial treatment initiation (pre-study).
10. Fulvestrant loading dose should be administered on Cycle 1 Day 15
11. cfDNA will be collected at: **baseline** (Cycle 1, Day 1), **Day 1 of every even cycle** after treatment initiation, and at the time of disease progression if the patient was still receiving study treatment at the time of disease progression. (**end-of-treatment**)
12. All subjects should have monthly Amsler grid tests and an **initial** ophthalmological examination performed at Screening by an ophthalmologist, which should include assessment of visual acuity, tonometry, fundoscopy (examination of both central and peripheral zones should be performed); where available, an Optical Coherence Tomography (OCT) should be performed. A **follow-up** ophthalmological examination should be performed as clinically necessary based on the findings of the monthly Amsler grid tests and clinical assessment. It is assumed that about 30% patients will require follow-up ophthalmological examinations.
13. When Central Serous Retinopathy (CSR)/Retinal Pigment Epithelial Detachments (RPED) is suspected, an OCT should be performed. Fluorescein angiography could be considered appropriate in conditions such as suspected Retinal Vein Occlusion (RVO). It is also recommended that color fundus photos or OCT images be obtained and stored in the subject's records for future reference. In subjects with suspected retinal pathology such as CSR or RVO, a consultation with a retina specialist should be considered.
14. Amsler grid testing will be administered by the treating physician or nurse on Day 1 of each 28-day cycle. Observation of wavy, broken or distorted lines, or reporting of a blurred/missing area of vision is equivalent to a positive Amsler grid test. For any positive Amsler grid test, subject should be referred for full ophthalmologic exam within 7 days. However, if the subject has an abnormal Amsler grid test at baseline (during Screening), then a repeat ophthalmic examination would be recommended only if, in the opinion of the investigator, there is a likelihood of significant change from the subject's baseline Amsler Grid test at Screening, or the subject has developed new clinical symptoms.
15. This tube of whole blood is necessary to be used as germline control once the Next Generation Sequencing is performed in the tissue collected. See **Lab Manual** for details.
16. Meal Record should be completed only on days of long PK assessments.
17. The 28 day follow-up visit will also be considered the off study visit for all patients removed for disease progression.
18. Patients removed from study drugs for reasons other than disease progression will be followed by chart review every three months until progression of disease occurs.

7. TREATMENT PLAN

7.1 Overview

This is an open-label, multi-institution, phase Ib (3+3 dose escalation design) that evaluates the safety profile (assessment of DLTs and MTD of the combination), tolerability and anti-tumor activity (progression-free survival [PFS] and lack of disease progression for ≥ 6 months [clinical benefit rate; CBR]) of fulvestrant, palbociclib and erdafitinib in patients with metastatic ER+/HER2-/*FGFR*-amplified breast cancer.

When feasible, a baseline biopsy of a metastatic site will be obtained for NGS and/or *FGFR* FISH prior to therapy initiation. Plasma will also be obtained at baseline, 4 weeks after treatment initiation and at disease progression for measurement of cfDNA. Treatment will be given until disease progression or unacceptable toxicity. To assess for anti-tumor effects, we will estimate the overall tumor burden at baseline to which subsequent measurements (performed every 8 weeks using the Solid Tumor Response Criteria [RECIST] v1.1) will be compared. Pharmacokinetic and pharmacodynamic studies will be obtained throughout the study.

7.2 Screening Phase

At screening, the patient will provide a signed informed consent form prior to any study related activities. Patients with known *FGFR1* amplification (by NGS, cfDNA or FISH) will require central confirmation of *FGFR1* amplification by FISH, but will not be required to wait for that result to initiate study treatment. Patients with known *FGFR2-4* amplification (by NGS, cfDNA or FISH) will not require central confirmation of *FGFR* amplification by FISH. Patients without known *FGFR* amplification will be screened for *FGFR1* amplification (as this is the most prevalent one) by FISH analysis at the Vanderbilt-Ingram Cancer Center (VICC). See Section 10 for details on tissue submission requirements and testing procedures. Once patients are deemed eligible, participants should begin study treatment consistent with the protocol as soon as possible but no later than 28 days after registration by the VICC Coordinating Center.

7.3 Agent Administration

The investigator will instruct the patient to take the study drugs as follows:

- Palbociclib: taken orally once daily, with food, for 21 days out of a 28-day cycle
- Erdafitinib: taken orally once daily, with ot without food, at approximately the same time every day, in a 28-day cycle
- Fulvestrant: IM once every 28 days (except on cycle 1, when fulvestrant will also be administered on day 15). On the days that patients come in for clinic visit/ fulvestrant administration on even cycles (i.e. when tumor measurements or PKs are done), administration of palbociclib and erdafitinib should wait to be done in clinic.

A pill diary will be given to all patients enrolled in the study.

1 cycle = 28 days				
N of pts.	**Dose Level**	**Fulvestrant (IM q28 days)[§]**	**Palbociclib* (PO daily x 21 out of 28 days)**	**Erdafitinib (PO daily)**

3-6	3	500 mg	125 mg	8 mg
3-6	2	500 mg	125 mg	6 mg
3-6	1	500 mg	125 mg	5 mg
3-6	–1	500 mg	125 mg	4 mg

* Palbociclib dose may be adjusted per standard of care clinical guidelines based on blood cell counts

§ On cycle 1, fulvestrant will also be administered on day 15 (loading dose)

7.3.1 Fulvestrant

Fulvestrant is FDA-approved for the treatment of ER+ MBC. It does not require specific prophylactic or supportive regimens. It is an intramuscular therapy that should be prepared according to manufacturer's recommendations.

Fulvestrant (500 mg) will be given on Day 1 and 15 in cycle 1 and then only Day 1 of each subsequent cycle during the treatment phase (± 3 days), in a 28-day cycle. Fulvestrant is administered intramuscularly, slowly, as two 5mL injections, one in each buttock. It can be administered with or without food.

On days when fulvestrant is administered, pharmacokinetic (PK) sampling should follow these additional guidelines:

- The pre-dose sample should be drawn just before fulvestrant dosing.
- The sampling time of the pre-dose PK sample and the dosing time of fulvestrant must be precisely recorded.

7.3.2 Palbociclib

Palbociclib is FDA-approved in combination with fulvestrant for the treatment of ER+ MBC. Administration is performed on an outpatient, self-administration basis, at a starting dose of 125 mg orally once daily, with food, on Days 1-21 followed by 7 days off treatment, in a 28-day cycle. Capsules of 75, 100 and 125 mg are available in case dose reductions are necessary (see Dose Modification guidelines, Section 8).

On days when patient is scheduled for a clinic visit, the patient should take scheduled palbociclib dose once all visit assessments have been performed and are within acceptable range) unless otherwise indicated. Patients should be instructed to record daily administration of the study drugs in the pill diary.

Missed doses of palbociclib should not be made up. For example, if a dose is vomited any time after taking palbociclib, a replacement dose should NOT be taken. If a dose is entirely missed for one day, dose should be skipped and NOT made up the next day; patients should resume regular dosing as prescribed the following day. Patients who inadvertently take one extra dose during a day must skip the next day's dose. If patient takes more than two doses of palbociclib in a day, the patient should bring this to the attention of his or her treating physician.

On days with PK sampling, the following additional guidelines should be followed:

- The pre-dose sample should be drawn before palbociclib dosing
- On days and time points when PK, biochemistry, hematology or other blood samples are to be performed, the PK sample must be drawn first
- The sampling time of the pre-dose PK sample and the dosing time of palbociclib must be precisely recorded

- If vomiting occurs, the exact time of the first vomiting episode within the first 4 hours post-dosing on that day must be noted
- Time of administration of gastric protection agents on days of PK sampling should be precisely recorded

7.3.3 Erdafitinib

Erdafitinib is an investigational product manufactured and provided by Janssen Research & Development, as film-coated tablets of 3, 4 and 5 mg. Administration is performed on an outpatient, self-administration basis, at a stipulated starting dose based on the escalation cohort level. Tablets should be swallowed intact, once daily, with 240 mL of water (8 ounces), with or without food, at approximately the same time every day, in a 28-day cycle. For dose adjustments, see Dose Modification guidelines, Section 8.

If a dose is missed, it can be taken up to 6 hours after the scheduled time. Otherwise, that dose should be skipped and subject should continue treatment at the scheduled time the next day. Missed doses of erdafitinib should not be made up. For example, if a dose is vomited any time after taking erdafitinib, a replacement dose should NOT be taken. If a dose is entirely missed for one day, dose should be skipped and NOT made up the next day; patients should resume regular dosing as prescribed the following day. Patients who inadvertently take one extra dose during a day must skip the next day's dose. If patient takes more than two doses of erdafitinib in a day, the patient should bring this to the attention of his or her treating physician.

On days when patient is scheduled for a clinic visit, the patient should take scheduled erdafitinib dose once all visit assessments have been performed and are within acceptable range unless otherwise indicated. Patients should be instructed to record daily administration of the study drugs in the pill diary.

On days with PK sampling, additional guidelines should be followed:

- The pre-dose sample should be drawn before erdafitinib dosing
- On days and time points when PK, biochemistry, hematology or other blood samples are to be performed, the PK sample must be drawn first
- The sampling time of the pre-dose PK sample and the dosing time of erdafitinib from the day before and current day must be precisely recorded
- If vomiting occurs, the exact time of the first vomiting episode within the first 4 hours post-dosing on that day must be noted
- Time of administration of gastric protection agents on days of PK sampling should be precisely recorded

7.4 Definition of Dose-Limiting Toxicity (DLT)

Any of the following events that occur during cycle 1 (first 4 weeks) will be considered a DLT when classified as possibly, probably or definitively related to investigational study treatment (according to NCI CTEP Adverse Event Reporting Requirements). Apart from the criteria listed below, if a lower grade AE leads to a dose interruption of more than 21 consecutive days of erdafitinib for the first 4 weeks of Cycle 1, this AE will be considered a DLT; patients must receive at least 75% of study drug during cycle 1 in order to be evaluable for the DLT observation period. Whenever a patient experiences toxicity that fulfills the criteria for a DLT, treatment with the study drug responsible for the toxicity will be interrupted (patient may continue the remainder study drugs) and the toxicity will be followed up. The Protocol Chair must be notified immediately of any DLT:

TOXICITY	DLT CRITERIA
Blood and lymphatic system disorders	Anemia CTCAE Grade ≥ 3 will not be considered DLT unless judged to be a hemolytic process secondary to erdafitinib.
	Febrile neutropenia CTCAE Grade ≥ 3
	ANC CTCAE Grade 3 for > 14 consecutive days
	ANC CTCAE Grade 4
	Platelet count CTCAE Grade 3 for > 7 consecutive days and/or with signs of bleeding
	Platelet count CTCAE Grade 4
Ocular disorders	CTCAE Grade ≥ 2 for > 21 days CTCAE Grade ≥ 3
General disorders and administration site conditions	Fatigue CTCAE Grade 3 for > 7 consecutive days
Skin and subcutaneous tissue disorders	Skin, mucosal or nail toxicity CTCAE Grade ≥ 3 for > 72 hours
Hyperphosphatemia	Phosphorus level ≥ 7.0 mg/dL for > 14 days despite treatment
GI disorders[a]	Diarrhea CTCAE Grade ≥ 3 for ≥ 48 hrs, despite the use of anti-diarrhea therapy
	Nausea/vomiting CTCAE Grade ≥ 3 for ≥ 48 hrs, despite the use of anti-emetic therapy
	Constipation CTCAE Grade ≥ 3 for ≥ 48 hrs, despite the use of anti-constipation therapy
Investigations[b]	Blood bilirubin[c] CTCAE Grade 2 for > 7 consecutive days or ≥ Grade 3
	AST or ALT CTCAE ≥ Grade 3
	Alkaline phosphatase CTCAE ≥ Grade 3
Other hematologic and non-hematologic toxicities	Any other CTCAE ≥ Grade 3 toxicity for > 7 consecutive days (except decreased lymphocyte count [lymphopenia] that is not clinically significant)

TOXICITY	DLT CRITERIA
[a] Patients will not initially receive prophylactic treatment for nausea/vomiting during Cycle 1. However, prophylactic treatment may be initiated in all patients at the dose level where these toxicities have been observed and in all further patients if at least 1 patient has experienced nausea/vomiting CTCAE Grade ≥ 3 or if at least 2 patients experienced nausea/vomiting CTCAE Grade ≥ 2. However, anti-emetics may be applied for treatment if the patient has experienced nausea/vomiting CTCAE Grade ≥ 1 at the discretion of the treating physician. [b] For any hepatic toxicity CTCAE Grade 4, or CTCAE Grade 3 that does not resolve within 7 days to CTCAE Grade ≤ 1 (or CTCAE Grade ≤ 2 if liver infiltration with tumor present), an abdominal CT scan should be performed to assess if it is related to disease progression. [c] Refers to total bilirubin. Apart from the criteria listed above, if a lower grade AE leads to a dose interruption of more than 14 consecutive days of erdafitinib, this AE **may** be considered as DLT (the determination will be based on clinical significance and patient risk; discussion with the Protocol Chair will determine if the event should or should not count as a DLT).	

Patients whose treatment is interrupted or permanently discontinued due to an AE or clinically significant laboratory value, must be followed as outlined in the table below, at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. Patients that require a dose delay of > 28 days due to a cause unrelated to study participation will have the opportunity to continue study if deemed eligible to do so by the Protocol Chair of the study.

TOXICITY	FOLLOW-UP EVALUATION
Hematology	If ≥ CTCAE grade 3 neutropenia or ≥ CTCAE grade 3 thrombocytopenia have been demonstrated, these parameters must be repeated at least once a week until resolution to ≤ CTCAE grade 1 neutropenia or ≤ CTCAE grade 1 thrombocytopenia to allow for initiation of re-treatment.
Renal	If creatinine ≥ 2 x ULN has been demonstrated, this parameter must be evaluated at least twice a week until resolution to ≤ CTCAE grade 1 to allow for initiation of re-treatment, and then at least weekly until either resolution or until stabilization.
	Creatinine ≥ 2.0 x ULN and 3+ proteinuria or hematuria ≥ CTCAE grade 2 has been demonstrated, a 24-hour urine collection for total protein and total creatinine must be repeated at least weekly until either parameter returns to baseline value or until stabilization. Whenever a measured CrCl is obtained, a creatinine should be obtained within ≤ 72 h of the urine collection.
Hepatic	If total bilirubin ≥ 2 x ULN or ≥ CTCAE grade 3 AST/ALT has been demonstrated, these parameters must be repeated daily until resolution to ≤ CTCAE grade 1 (or ≤ grade 2 for AST or ALT, if liver metastasis are present) to allow for initiation of re-treatment, and then at least weekly until either resolution or until stabilization
	Patients with total bilirubin > ULN (any duration) should have fractionation of bilirubin into total/direct or indirect/direct components and any additional work-up as clinically indicated by

	these results. Follow-up of hyperbilirubinemia should proceed as per the guidelines above, irrespective of the results of fractionation.
Metabolic/Laboratory	Parameters of metabolic/ laboratory abnormalities ≥ CTCAE grade 3 must be assessed once at 2 to 4 days and once again at 7 days (± 1 day) and be repeated twice a week until resolution to ≤ CTCAE grade 2 to allow for initiation of re-treatment, and then at least weekly until either resolution to ≤ CTCAE grade 1 or until stabilization.
	A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥ CTCAE grade 3 of amylase or lipase levels.
	In patients with triglycerides ≥ 500 mg/dL, urine amylase needs to be tested in addition.
Ocular toxicity	Patients who experience ocular toxicity should be followed as per Dose Modification guidelines (Section 8)
Non-Laboratory	Patients who experience non-laboratory DLTs must be evaluated at least once a week following demonstration of the toxicity until resolution of the toxicity to allow for re-treatment, stabilization of the toxicity, or study treatment completion.

7.5 Definition of Maximum Tolerated Dose (MTD)

The MTD will be defined as the highest dose at which 20% of the patients experienced a DLT. The first cohort of patients (3 patients) will be started at dose level 1, and each patient will be observed for 4 weeks on the specified dose. No new cohort of patients will be treated until the previous cohort has been fully evaluated for toxicity and a dose escalation decision has been made. Routine updates regarding patient and study status will be conducted.

Once the MTD is reached, the safety data will be analyzed and the expansion component of the study will be completed to assess tolerability and efficacy. Patients in the phase II portion of the study will initiate study treatment at the MTD defined in the escalation component of the trial. Note that dose reduction within patients (individually) is allowed after the 4 week DLT observation period in the escalation and in the expansion components of the study (see Dose Modification guidelines, Section 8). Intrapatient dose escalation will not be allowed. Dose reduction will be required for a given patient in case of:

- Grade 3 or 4 toxicities
- Grade ≥ 2 hyperphosphatemia lasting more than 21 days despite medical treatment, or
- Grade ≥ 2 ocular toxicity lasting more than 28 days despite medical treatment, or
- Grade ≥ 2 elevation of creatinine, bilirubin, AST, or ALT lasting more than 14 days despite medical treatment, or
- Grade ≥ 2 skin or nail toxicity for more than 28 days in a row despite optimal medical treatment, or

- Grade ≥ 2 GI toxicity lasting more than 14 days despite medical treatment.

7.6 Concomitant Treatment and Supportive Care Guidelines

Because there is a potential for interaction of erdafitinib and palbociclib with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Protocol Chair should be alerted if the patient is taking any agent known to affect or with the potential to affect selected P450 isoenzymes (Cautionary Concomitant Medications list). Patients taking any of the medications on the Cautionary Concomitant Medications list are enrouraged to seek alternative medications; if not possible, patient will not necessarily be excluded from entering the study, but approval by the Study Chair has to be obtained prior to enrollment. Patients already enrolled in the study that initiate and persist taking any of the medications on the Cautionary Concomitant Medications list will also require approval from the Study Chair.

Patients on chronic medications that can be given concomitantly with erdafitinib and palbociclib should be maintained on the same dose and dose schedule throughout the study period, as medically feasible. The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug, and any changes in dosing should be recorded.

All supportive measures consistent with optimal patient care can be given throughout the study at the discretion of the treating physician, as long as they are not part of the list of prohibited medications. In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted with the following considerations:

- Prophylactic anti-emetics should be started only once the patient experienced nausea or vomiting at the discretion of the investigator.
- There are no concurrent supportive or prophylactic growth factor support regimens recommended for palbociclib. While the rates of grade III/IV neutropenia are considerable with CDK4/6 inhibitors, the rates of febrile neutropenia (FN) are quite low, and well below the 20% threshold for which FN prophylaxis with G-CSF is recommended. Nonetheless, G-CSF support will be allowed at the treating physician's discretion. Hematopoietic growth factors may be used according to ASCO guidelines
- Bone directed therapy to prevent skeletal related events (SRE's) or to treat osteoporosis with bisphosphonates or denosumab is permitted. While the use of bisphosphonates has been found to reduce the incidence of new bone metastases in patients with metastatic breast cancer, we do not anticipate this to affect the results of this trial. Thus, treatment initiated prior to registration or after registration with these agents is permitted. The time of initiation of bone directed therapy should be clearly recorded on the case report forms
- Local radiotherapy required for life-threatening situations (e.g., superior vena cava syndrome, spinal cord compression, central nervous system metastases) will require the patient to discontinue protocol treatment due to symptomatic deterioration. However, limited palliative radiotherapy (i.e., to bone metastasis) in subjects who are otherwise benefiting from study treatment will be allowed during the study but must be discussed with the Protocol Chair. Study treatment should be withheld until palliative radiotherapy is terminated. This treatment break should not be considered as treatment interruption. Palliative radiation is permitted if done solely for bone pain relief. It should not be delivered to a target lesion and it should not encompass more than 25% of irradiated bone marrow. If palliative radiotherapy is initiated

after the start of study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be ruled out

- Other investigational therapies must not be used while the patient is on the study
- Anticancer systemic therapy other than the study treatments must not be given to patients while on the study. If such agents are required for a patient then the patient must be discontinued from the study
- Medications known to increase serum levels of phosphate, such as potassium phosphate supplements (oral or IV), vitamin D supplements, antacids, and phosphate-containing enemas and laxatives (oral/rectal) thought to increase serum phosphate levels. Medications known to have phosphate as an excipient should be avoided unless no alternatives exist
- Herbal preparations are not allowed throughout the study. These herbal preparations include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal preparations 14 days prior to first dose of study drug

7.7 Duration of Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue until one of criteria in Section 7.9 applies.

7.8 Duration of Follow-Up

Participants will have a follow up at 28 days (± 7days) after discontinuation of study drugs for any reason (unacceptable adverse events or disease progression) for toxicity assessments.

- Participants removed from study for unacceptable adverse events will be followed weekly until resolution or stabilization of a serious adverse event, and will be followed every three months (chart review) until disease progression, or until death from any cause (whichever occurs first)Patients continuing fulvestrant who have discontinued erdafitinib or palbociclib for any reason other than disease progression will be followed until disease progression as stated above

7.9 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 7.10 applies. All patients who initiate protocol treatment will be included in the safety analysis, and all patients who initiate protocol treatment and receive at least 8 weeks of treatment will be included in overall evaluation of response. All reasons for discontinuation of therapy should be documented clearly in the medical record.

7.10 Discontinuation of Treatment

The reasons for discontinuation or protocol treatment include:

- Evidence of disease progression during treatment at the discretion of the treating investigator
- Non-compliance with the study protocol, including, but not limited to not attending the majority of scheduled visits. The Protocol Chair will determine when non-compliance should lead to removal from study. Note: These patients will still be included in the overall evaluation of safety and response
- Unacceptable major toxicity. Note: These patients will still be included in the overall evaluation of safety and response

- Intercurrent illness or condition that would, in the judgment of the treating investigator, affect assessment of clinical status to a significant degree or require discontinuation of study treatment
- At subject's own request. Note: The reason for discontinuation from the study must be documented. These patients will be included in the overall evaluation of safety and response if any protocol therapy was administered prior to withdrawal
- Study is closed for any reason (e.g. new information shows that the patient's welfare would be at risk if she continued study treatment)
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator
- Patients that require a dose delay of > 28 days. If the delay is due to a cause unrelated to study participation, the patient will have the opportunity to continue study if beyond the first 8 weeks of treatment, if clinical benefit is seen, and if deemed eligible to do so by the Protocol Chair of the study
- If the patient requires dose reduction below dose level -1, the patient should be discontinued from the study unless deemed to have clinical benefit that would outweigh the risk. A discussion with the Protocol Chair should be carried out prior to final decision on discontinuation

7.11 Replacement of Patients Who Discontinue Early

In general, the study intends that patients would be treated until disease progression or intolerable toxicity. During the phase Ib dose escalation period and phase II portion of the study, if a patient discontinues study treatment for reasons clearly not related to study treatment, after completing fewer than one planned cycle of study, and/or receiving <75% of the total intended dose of study drugs over the first cycle of treatment, then that patient will be considered not evaluable and may be replaced with a new patient.

7.12 Withdrawal from Study

The reasons for withdrawal from the study include:

- Subject withdraws consent for follow-up
- Subject is lost to follow-up
- Study is terminated for any reason

8. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

8.1 Erdafitinib

8.1.1 Most common anticipated toxicities (refer to IB for further details)

- Hyperphosphatemia
- Decrease in appetite
- Dry mouth
- Nail and skin toxicities
- Palmar-plantar erythrodysthesia
- Mucositis (mouth sores)
- Dysgeusia
- Constipation
- Diarrhea
- Fatigue/asthenia

- Reversible retinal pigment epithelial detachment (RPED or central serous retinopathy [CSR])
- Nausea

8.1.2 Adverse events of special interest

Central serous retinopathy was reported in 52 subjects (10.4%) across 5 studies at all doses and 32 subjects (14.4%) at the 8 or 9 mg dose. Events of CSR included preferred terms of , retinal detachment (18 subjects), chorioretinopathy (15 subjects), detachment of retinal pigment epithelium (11 subjects) and retinal edema (5 subjects). Most events were Grade 1 or Grade 2 (data cut-off 4 June 2019, IB v. 8). Drug-induced CSRs are generally reversible.

8.1.3 Adverse events of clinical importance

8.1.3.1 Skin, mucosal, and nail changes

Skin, mucosal and nail toxicities are commonly reported in erdafitinib studies. Nail toxicity were reported in 44.3% of subjects at all doses (56.8% at the 8 or 9 mg dose) and skin toxicityin 42.3% of subjects (45.9% at the 8 or 9 mg dose) from 5 poled studies (data cut-off June 2019, IB v 8). . While frequent and known to be associated with FGFR inhibitors, these toxicities respond well to medical management and did not necessitate permanent changes in treatment.

General recommendations to avoid skin toxicities:

- Avoid unnecessary exposure to sunlight and excessive use of soap.
- Avoid bathing in excess; use tepid rather than hot water.
- Use moisturizers regularly; apply thick, alcohol-free and oil-in-water based emollient cream on exposed and dry areas of the body.
- Avoid perfumed products, bubble bath, perfumed soaps, and take breaks from shaving.
- Use broad-spectrum sunscreen with a skin protection factor (SPF) ≥15.
- Wear cotton clothes next to skin rather than wool, synthetic fibers, or rough clothing.
- Use occlusive alcohol-free emollient creams (jar or tub) for treatment of mild/moderate xerosis.
- For scaly areas, use exfoliants (ammonium lactate 12% or lactic acid cream 12%).

General recommendations to prevent mucositis:

- Good oral hygiene
- Use a soft toothbrush
- Avoidance of spicy, acidic, hard, and hot food and beverages
- Use of mild-flavored toothpastes
- Use of saline-peroxide or salt and soda mouthwashes 3 or 4 times per day
- Water soluble lubrication agents like artificial saliva (for xerostomia or dry mouth)

General recommendations to prevent nail toxicities:

- Good hygienic practices, keep fingers and toes clean.
- Keep nails trimmed
- Use gloves for housecleaning and gardening to minimize damage and prevent infection
- Nail polish and imitation fingernails should not be worn until the nails have grown out and returned to normal
- Wearing comfortable shoes (wide sized shoes with room for the toes)
- Trimming nails but avoiding aggressive manicuring

8.1.3.2 Hyperphosphatemia

Hyperphosphatemia, an expected class effect of FGFR inhibitors, was the most frequently reported AE of clinical importance in Study EDI1001 (65.2% of subjects, Table 49 of IB) and in Study BLC2001 (54.3% of subjects,Table 50 of IB). To further understand the occurrence of hyperphosphatemia, an analysis of serum phosphate levels was conducted in Study EDI1001. The average baseline phosphate level for 187 subjects across tumor types was 3.4 mg/dL with a median of 3.4 mg/dL and range of 1.5-5.2 mg/dL. The profile of mean percent change in phosphate levels over time showed phosphate levels peaked between Cycles 1 and 2 of treatment with erdafitinib. Increases in phosphate were dose dependent; at 9 mg daily, the maximum mean phosphate concentration was 7.3 mg/dL on Cycle 1 Day 21. The trend in mean phosphate levels showed a decline in phosphate level changes from baseline over time beginning at approximately Cycle 3 of treatment. Thus maximum phosphate elevations were transient and serum phosphate levels stabilized even with continued exposure to erdafitinib. If use of a phosphate binder is required and sevelamer hydrochloride (Renagel) is not available, use of other phosphate binders (non–calcium containing) based on the local standard is recommended, including Sevelamer carbonate (Renvela) or lanthanum carbonate (Fosrenol).

8.1.3.3 Arrhythmias

Arrythmia is no longer an AE of clinical importance. Due to the preclinical signal, arrhythmias remain were designtated as clinically important; however, the potential cardiac liability of erdaftinib has not been observed in clinical studies. A review of the QTcF intervals and the pharmacokineticpharmacodynamic relationships for erdafitinib revealed no effects of erdafitinib on cardiac repolarization or other electrocardiographic parameters. Thus the potential cardiac liability of erdafitinib has, to date, not been observed in clinical studies.

8.1.3.4 Ocular toxicities

Ocular toxicities such as dry eyes, keratitis and reversible retinal pigment epithelial detachment (RPED or central serous retinopathy [CSR]/ choroidopathy) have been noted with erdafitinib and other FGFR inhibitors. Eye toxicity was reported by 41.1% of subjects in at all doses from 5 studies(data cut-off June 2019, IB v8), the most common events (≥ 5% overall were dry eye, lacrimation increased, vision blurred, and conjunctivitis.

Retinal pigment epithelial detachment is the separation of the retinal pigment epithelium (RPE) from the Bruch's membrane due to the presence of sub-RPE fluid, blood, fibrovascular membrane, or drusenoid material and is attributed to the disruption of the ionic pump of the RPE cells or hyperpermeability of the choroidal vasculature. Drug- induced RPED/CSRs are generally reversible.

8.1.3.4.1 Assessment and evaluation plan for new subjects and subjects during study without ocular symptoms

All patients exposed to erdafitinib should have a baseline assessment of visual acuity, tonometry, fundoscopy (examination of both central and peripheral zones should be performed) and Amsler Grid test, and, where available, an optical coherence tomography (OTC) should be performed. The ophthalmological test should be performed once during screening. Additional exams should be performed as clinically necessary based on the findings of the Amsler grid test and clinical assessment.

An Amsler grid test should be performed at the beginning of every new cycle and at the end of treatment, to identify any new abnormalities (observation of wavy, broken or distorted lines or a blurred or missing area of vision).

- If the subject is asymptomatic and the Amsler grid test is negative, patient will continue study medication at current dose and schedule.
- If the subject is asymptomatic and the Amsler grid test is positive (observation of wavy, broken or distorted lines or a blurred or missing area of vision) then the subject should have a full ophthalmological exam as described, within 7 days. If this is not possible then the study drug should be withheld until a full ophthalmological exam is performed.
- If the subject has ocular abnormalities, manage as per the Dose Modification guidelines for ocular toxicity (Section 8.4).

8.1.3.4.2 Assessment and evaluation plan for any subject during study with ocular symptoms

Subjects that have ocular symptoms at any time should be managed as per the “Management Guidelines for Eye Toxicity Associated with Vision Changes”.

Additional modification to the type and or frequency of these exams could be made based on emerging data and/or in consultation with regulatory agencies. If and when such changes are made they will be communicated and incorporated into existing protocols.

When central serous retinopathy (CSR)/retinal pigment epithelial detachments (RPED) is suspected then an OCT should be performed. Fluorescein angiography could be considered appropriate in conditions such as suspected retinal vein occlusion (RVO). It is also recommended that color fundus photos or OCT images be obtained and stored in the patient’s file for future reference. In patients with suspected retinal pathology such as CSR or RVO a consultation with a retina specialist should be considered.

8.1.3.4.3 Management Guidelines for Eye Toxicity Associated With Vision Changes

Eye toxicities considered a consequence of dry eye should be managed as per the standard clinical practice and as per the standard toxicity management guidelines described in the protocol. Subjects with confirmed new corneal or retinal abnormality while taking the study medication should be reported with an AE of special interest (Grade 1 and 2) or SAE (Grade ≥3) as appropriate.

Any new eye symptoms of clinical significance such as but not limited to blurred vision, partial or complete loss of vision, double vision, floaters or color spots or halos around light, change in color or night vision, photophobia, ocular pain or stinging sensation, and foreign body sensation should be further evaluated and managed as per the Dose Modification guidelines for ocular toxicity (Section 8.4).

8.1.3.4.4 Guidelines for the management of dry eye

- General considerations: Avoid unnecessary exposure to sunlight, use sunglasses in bright light.
- Prophylactic management: Frequent use of artificial tear substitutes is strongly recommended.
- Reactive management:
  - Withhold erdafitinib for Grade 3 toxicity
  - Artificial tear substitutes if not started, every 4 to 6 hours
  - Hydrating /lubricating eye gels and ointments
  - Severe treatment-related dry eye should be evaluated by an Ophthalmologist

8.2 Fulvestrant

8.2.1 Most common anticipated toxicities (refer to package insert for further details)

- Hot flashes
- Joint disturbances
- Injection site reactions
- GI disturbances

There is considerable clinical experience with fulvestrant 500 mg intramuscular dosing every 4 weeks (with an initial loading dose phase at cycle 1 day 15); it is generally very well tolerated. As was clearly established in the CONFIRM trial, the higher dose of fulvestrant 500 mg is more efficacious than the lower dose of 250 mg, with essentially no difference in adverse event rates. Dose reduction to 250 mg is left to the discretion of the treating physician, but it is not anticipated that dose reduction will improve adverse effects and it should generally be avoided given the inferior efficacy. However, dose reduction to fulvestrant 250 mg can be considered in patients with moderate hepatic impairment.

8.3 Palbociclib

8.3.1 Most common anticipated toxicities (refer to package insert for further details)

- Neutropenia
- Leukopenia
- Anemia
- Thrombocytopenia
- Fatigue
- Nausea

The primary anticipated toxicity of palbociclib is neutropenia. In the phase I trials of palbociclib alone in patients with advanced cancers, neutropenia was the only dose-limiting toxicity (DLT). Grade 3 neutropenia during cycle 1 was observed in 3/22 patients receiving palbociclib 125 mg PO daily, with no grade 4 neutropenic events observed. Based on this result, 125 mg PO daily became the recommended phase II dose (RP2D). Other hematologic AEs of grade 3 or greater during cycle 1 were anemia and leukopenia, occurring in 1 and 4 of 41 patients, respectively. The most common non-hematologic AEs of grade 3 or greater during cycle 1 were fatigue, nausea, and abdominal pain (each occurring in 2 of 41 patients). Of note, there were no complicated hematologic AEs documented, and all hematological AEs resolved during the off drug period of a 3 week on/1 week off schedule, and were non-cumulative.

In a phase II trial of palbociclib alone for advanced breast cancer, the only toxicities grade ≥3 observed were transient neutropenia (50%) and thrombocytopenia (21%). In a phase II trial of palbociclib plus letrozole for first-line therapy of ER+ MBC, the most common AEs reported were neutropenia, leukopenia, and fatigue. The median time to first treatment delay for neutropenia was 58 days, and the median duration of treatment delay until recovery was 5 days (range 1-16 days). In general, hematological abnormalities were adequately managed with standard supportive care, were not complicated, and resolved during the drug hold with no cumulative toxicity noted. In the phase I dose-escalation trial of palbociclib alone, QT interval changes were also evaluated in detail. While 26 of 41 patients had a maximum increase of <30 msec from baseline QTc, no patients had an on-treatment value exceeding 500 msec.

8.3.2 Dose Modification/ Delays and Toxicity Management

In the event of significant treatment-related toxicity, palbociclib and erdafitinib dosing may be interrupted or delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify investigators at the first occurrence of any adverse sign or symptom. Patients should not hold or discontinue palbociclib and erdafitinib for side effects potentially or likely related to concomitant anti-hormonal therapy (e.g., grade 3 or long lasting grade 2 joint pain) as per the investigator's judgment.

Missed doses are not made up. When the adverse event resolves, the cycle will continue as scheduled. However, if palbociclib or erdafitinib start for a specific cycle is delayed for toxicity, fulvestrant will continue without change.

The need for a dose reduction at the time of treatment resumption should be based on the table criteria below unless expressly agreed otherwise following discussion between the investigator and the Protocol Chair. If a dose reduction is applied, the patient may need to return to the clinic to receive new drug supply.

8.4 Palbociclib and Erdafitinib Dose Modifications and Management of Toxicities

Palbociclib dose level reductions			
Starting dose	**First reduction**	**Second reduction**	**Third reduction**
125 mg	100 mg	75 mg	Discontinue if no clinical benefit has been seen

Erdafitinib dose level reductions				
Starting dose	**First reduction**	**Second reduction**	**Third reduction**	**Fourth reduction**
8 mg	6 mg	5 mg	4 mg	Discontinue if no clinical benefit has been seen
6 mg	5 mg	4 mg		Discontinue if no clinical benefit has been seen
5 mg	4 mg	Discontinue if no clinical benefit has been seen		

Investigations – Hematology (for palbociclib only)	
ANC decreased (Neutropenia)	
Grade 1 / 2	Maintain dose level of palbociclib.
Grade 3	Omit dose of palbociclib until ANC ≥ 1000/mm^3, then - If resolved in ≤ 7 days, then maintain dose level of palbociclib. - If resolved in > 7 days, then ↓ 1 dose level of palbociclib.
Grade 4	Omit dose of palbociclib until ANC ≥ 1000/mm^3, then ↓ 1 dose level of palbociclib. Erdafitinib should be omitted as well if the treating physician considers that the safety of the patient is compromised.
Anemia	
Grade 1 / 2	Maintain dose level of palbociclib.
Grade 3	Omit dose of palbociclib until resolved to CTCAE Grade ≤ 2, then maintain dose level of palbociclib
Grade 4	Discontinue palbociclib.
Febrile neutropenia	
Grade 3	Omit dose of palbociclib, then

	- If resolved by ≤ 7 days, then, ↓ 1 dose level of palbociclib. - If not resolved within 7 days discontinue palbociclib.
Grade 4	Discontinue palbociclib. Erdafitinib shoud be omitted as well if the treating physician considers that the safety of the patient is compromised.
Platelet count decreased (Thrombocytopenia)	
Grade 1 / 2	Maintain dose level of palbociclib.
Grade 3	Omit dose of palbociclib until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then ↓ 1 dose level of palbociclib. - If resolved in > 7 days and/or with signs of bleeding, then discontinue patient from palbociclib.
Grade 4	Discontinue palbociclib.
Bleeding	
Any bleeding (related to palbociclib) resulting in platelet transfusion	Omit dose of palbociclib until no further bleeding has been observed. Continuation of study treatment may be considered based on the thrombocytopenia recommendations.
Investigations – Hepatic	
Total bilirubin **(for patients with Gilbert syndrome these dose modifications apply to changes in direct bilirubin only)**	
Grade 1	Maintain dose level of palbociclib and erdafitinib.
Grade 2	Omit dose of palbociclib and erdafitinib, and check bilirubin daily until resolved to CTCAE Grade ≤ 1, then: - If resolved in ≤ 7 days, then maintain dose level of palbociclib and erdafitinib. - If resolved in > 7 days, then ↓ 1 dose level of palbociclib and erdafitinib. Start palbociclib first, and recheck bilirubin level in 7 days. If level remains CTCAE Grade ≤ 1, then reintroduce erdafitinib.
Grade ≥ 3	Discontinue palbociclib and erdafitinib.
Note: If CTCAE Grade 3 or 4 hyper-bilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g. review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level of palbociclib and erdafitinib and continue treatment at the discretion of the Investigator.	
AST or ALT	
Grade 1	Maintain dose level of palbociclib and erdafitinib.
Grade 2	Omit dose of palbociclib and erdafitinib, and check AST and ALT daily until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then maintain dose level of palbociclib and erdafitinib - If resolved in > 7 days, then ↓ 1 dose level of palbociclib and erdafitinib. Start palbociclib first, and recheck AST and ALT levels in 7 days. If levels remain CTCAE Grade ≤ 1, then reintroduce erdafitinib.
Grade 3	Omit dose of palbociclib and erdafitinib, and check AST and ALT daily until resolved to CTCAE Grade ≤ 1 (or CTCAE Grade ≤ 2 in case of liver metastasis), then - If resolved in ≤ 7 days, then ↓ 1 dose level of palbociclib and erdafitinib. Start palbociclib first, and recheck AST and ALT levels in 7 days. If levels remain CTCAE Grade ≤ 1, then reintroduce erdafitinib. - If resolved in > 7 days, then discontinue patient from palbociclib and erdafitinib
Grade 4	Discontinue palbociclib and erdafitinib.

AST or ALT and Bilirubin	
AST or ALT > 3.0 – 5.0 ULN and total bilirubin > 2.0 x ULN	Omit dose of palbociclib and erdafitinib, , and check bilirubin, AST and ALT daily until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, then ↓ 1 dose level of palbociclib and erdafitinib. Start palbociclib first, and recheck bilirubin, AST and ALT levels in 7 days. If levels remain CTCAE Grade ≤ 1, then reintroduce erdafitinib. - If resolved in > 7 days, then discontinue patient from palbociclib and erdafitinib.
AST or ALT > 5.0 ULN and total bilirubin > 2.0 x ULN	Discontinue palbociclib and erdafitinib.
Metabolism and nutrition disorders (for erdafitinib only)	
Phosphorus elevation[a]	
5.5-6.9 mg/dL	Maintain dose level of erdafitinib. May consider sevelamer 800 mg to 1,600 mg 3 times a day (with food).
7.0-9.0 mg/dL	Omit erdafitinib. Sevelamer 800 to 1,600 mg 3 times a day with food until phosphate level is <5.5 mg/dL. Once serum phosphate level returns to <5.5 mg/dL, restart erdafitinib at same dose level. A dose reduction may be implemented for persistent hyperphosphatemia (≥7 mg/dL) if clinically necessary
>9.0 mg/dL	Omit erdafitinib. Sevelamer up to 1,600 mg 3 times a day with food AND Acetazolamide 250 mg 2 or 3 times a day only until serum phosphate level returns to <5.5 mg/dL. Once serum phosphate level returns to <5.5 mg/dL, restart treatment at the first reduced dose level. A second dose reduction may be implemented if needed or clinically indicated for persistent hyperphosphatemia (≥7 mg/dL) at every cycle
>10.0 mg/dL and/or significant alteration in baseline renal function and/or Grade 3 hypocalcemia	Erdafitinib should be discontinued permanently. (In situations where the subject is having clinical benefit and the investigator and the Study Chair agree that re-starting drug is in the best interest of the subject, the drug may be re-introduced at 2 dose levels lower if appropriate. Follow other recommendations described above.
[a]*Note:* Restriction of phosphate intake to 600 – 800 mg/day is recommended to all subjects in the study	
Ocular toxicity (for erdafitinib only)	
Grade 1	Refer to ophthalmologic exam. If this cannot be performed within 7 days, omit erdafitinib until an exam can be performed. If no evidence of eye toxicity, continue erdafitinib at same dose level.

	If keratitis or retinal abnormality are detected, omit erdafitinib until signs and symptoms have resolved; follow specific treatment as per ophthalmologist's recommendations. For retinal pathology perform OTC as appropriate and consider referral to a retina specialist for further evaluation. If toxicity is reversible (complete resolution or stabilization and asymptomatic) in 4 weeks according to ophthalmologic exam, resume erdafitinib at the next lower dose level after consultation with Protocol Chair. Monitor for recurrence every 1 to 2 weeks for a month and as clinically appropriate thereafter. If there is no recurrence then re-escalation can be considered in consultation with the medical monitor. If there is no evidence of eye toxicity, continue erdafitinib therapy at the same dose level.
Grade 2	Immediately omit erdafitinib and refer to ophthalmologic exam. If keratitis or retinal abnormality are detected, omit erdafitinib until signs and symptoms have resolved; follow specific treatment as per ophthalmologist's recommendations. For retinal pathology perform OTC as appropriate and consider referral to a retina specialist for further evaluation. Monitor for recurrence every 1-2 weeks for a month and **as clinically appropriate thereafter.** If toxicity is reversible (complete resolution or stabilization and asymptomatic) in 4 weeks according to ophthalmologist exam, resume erdafitinib at the next lower dose level if patient is deriving clinical benefit from treatment, after consultation with Protocol Chair.
Grade 3	Immediately discontinue erdafitinib, refer to ophthalmologic exam, report as SAE. If keratitis or retinal abnormality are detected, omit Erdafitinib until signs and symptoms have resolved; follow specific treatment as per ophthalmologist's recommendations. For retinal pathology perform OTC as appropriate and consider referral to a retina specialist for further evaluation. If toxicity is reversible (complete resolution or stabilization and asymptomatic) in 4 weeks according to ophthalmologist exam, resume erdafitinib at 2 lower dose levels if patient is deriving clinical benefit from treatment, after consultation with Protocol Chair. Continue to monitor for recurrence of toxicity every 1-2 weeks for a month and as clinically appropriate thereafter, using appropriate investigations. For cases of recurrence, permanently discontinue erdafitinib.
Grade 4	Immediately discontinue erdafitinib permanently, refer to ophthalmologic exam, report as SAE. Continue to monitor for recurrence of toxicity every 1-2 weeks for a month and as clinically appropriate thereafter, using appropriate investigations.
GI disorders	
Constipation (for erdafitinib only)	
Grade 1	Maintain dose level of erdafitinib, but initiate anti-constipation treatment.
Grade 2	Omit dose of erdafitinib until resolved to CTCAE Grade ≤ 1, then maintain dose level of erdafitinib.

Grade 3	Omit dose of erdafitinib until resolved to CTCAE Grade ≤ 1, then reduce dose of erdafitinib by 1 dose level.
Grade 4	Discontinue erdafitinib.
Diarrhea (for palbociclib only)	
Grade 1	Maintain dose level of palbociclib, initiate anti-diarrhea treatment per standard practice.
Grade 2	Initiate anti-diarrhea treatment per standard practice. Omit dose of palbociclib until resolved to CTCAE Grade ≤ 1, then maintain dose level of palbociclib. For 2nd occurrence of diarrhea CTCAE Grade 2, omit dose of palbociclib until resolved to CTCAE Grade ≤ 1, then reduce palbociclib by 1 dose level.
Grade 3	Initiate anti-diarrhea treatment per standard practice. Omit dose of palbociclib until resolved to CTCAE Grade ≤ 1, then reduce dose of palbociclib by 1 dose level. For 2nd occurrence of diarrhea CTCAE Grade 3, discontinue palbociclib.
Grade 4	Initiate anti-diarrhea treatment per standard practice. Discontinue palbociclib.
Note: Antidiarrheal medication per standard practice is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea.	
Mucositis	
Grade 1	Continue palbociclib and erdafitinib at same doses. Topical steroid moderate strength and lidocaine 2-5% jelly or solution QID.
Grade 2	Continue palbociclib and erdafitinib at current dose. Dexamethasone solution (3.3 mg/5 mL) swish and spit QID and lidocaine 2-5% jelly or solution QID. Consider study drug holding if no improvement in 1 week. When resolves to ≤Grade 1 or baseline, restart at same or 1 dose level below in consultation with the medical monitor.
Grade 3	Hold palbociclib and erdafitinib (for up to 28 days), with weekly reassessments of clinical condition. Dexamethasone solution (3.3 mg/5 mL) swish and spit QID and lidocaine 2-5% jelly or solution QID When resolves to ≤Grade 1 or baseline, restart at 1 dose level below in consultation with the medical monitor.
Grade 4	Discontinue palbociclib and erdafitinib; evaluation and therapy as clinically indicated.
Skin and subcutaneous disorders (for erdafitinib only)	
Skin toxicity	
Grade 1	Maintain dose level of erdafitinib. Use fragrance free moisturizing cream or ointment BID over entire body. Use ammonium lactate 12% cream or salicylic acid 6% cream BID over dry/scaly/hyperkeratotic areas such as palms and soles.

Grade 2	Maintain dose level of erdafitinib. Use fragrance free moisturizing cream or ointment BID over entire body. Use ammonium lactate 12% cream or salicylic acid 6% cream BID over dry/scaly/hyperkeratotic areas such as palms and soles. Use zinc oxide 13-40% at night for areas with fissures.
Grade 3	Omit erdafitinib doses for up to 28 days, with weekly assessments of clinical condition. Use topical steroid ointment or cream (Clobetasol 0.05%, Betamethasone 0.05%, Fluocinonide 0.05%) BID and zinc oxide 13-40% at night for areas with fissures. Once resolved to grade ≤ 1 then: - If resolved in ≤ 14days, ↓ 1 dose level of erdafitinib. - If resolved in > 14 days, discontinue patient from erdafitinib.
Grade 4	Discontinue erdafitinib; therapy as clinically indicated.
Nail toxicity	
Grade 1	Maintain dose level of erdafitinib. Over the counter nail strengthener OR poly-urea urethane nail lacquer (Nuvail) OR diethylene glycol monoethylether nail lacquer daily (Genadur).
Grade 2	Maintain dose level of erdafitinib. For signs of infection (periungal edema/erythema/ tenderness and/or discharge), start the following: - treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/ trimethoprim (Bactrim®) DS BID) AND - topical antifungal lacquer daily for 6+ weeks (ciclopirox olamine 8% OR efinaconazole 10% OR amorolfine 5% weekly OR bifonazole/urea ointment daily) Consider study drug holding if no improvement in 1 to 2 weeks. When resolved to ≤ Grade 1 or baseline, restart at same or 1 dose level below in consultation with the medical monitor.
Grade 3	Hold erdafitinib (for up to 28 days), with weekly reassessments of clinical condition. Silver nitrate application weekly AND topical antibiotics (Mupirocin 2%, gentamycin, bacitracin zinc/polymixin B) AND vinegar soaks (soaking fingers or toes in a solution of white vinegar in water 1:1 for 15 minutes every day). For signs of infection (periungal edema/erythema/ tenderness and/or discharge), start the following: treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/trimethoprim (Bactrim®) DS BID). For cases of severe/refractory infection consider intravenous antibiotics. Consider dermatological and/or surgical evaluation if necessary. When resolved to ≤Grade 1 or baseline, restart at 1 dose level below in consultation with the medical monitor.

Grade 4	Discontinue erdafitinib, evaluation and therapy as clinically indicated.
General disorders (for erdafitinib only)	
Fatigue/ asthenia	
Grade 1 / 2	Maintain dose level of erdafitinib.
Grade 3	Omit dose of erdafitinib until resolved to CTCAE Grade ≤ 1, then - If resolved in ≤ 7 days, maintain dose level of Erdafitinib. - If resolved in > 7 days, discontinue patient from Erdafitinib.
Other AEs	
Grade 1 / 2	Maintain dose level of palbociclib and erdafitinib.
Grade 3	Omit dose of palbociclib and erdafitinib until resolved to CTCAE Grade ≤ 1, then ↓ dose level of palbociclib and erdafitinib.
Grade 4	Discontinue palbociclib and erdafitinib.

- All dose modifications should be based on the worst preceding toxicity. Once a dose has been reduced it will not be increased at a later time even if there is no toxicity. Patients who require dose reductions of palbociclib and erdafitinib past the lowest dose level will be discontinued from study drugs treatment.
- If a patient requires a dose delay of > 28 consecutive days from the intended day of the next scheduled dose of palbociclib and erdafitinib, due to study related interventions, then the patient must be discontinued from the study treatment. Patients that require a dose delay of > 28 days due to a cause unrelated to study participation will have the opportunity to continue study if deemed eligible to do so by the Protocol Chair of the study. Patients who discontinue from the study for a study-related AE or an abnormal laboratory value must be followed at least once a week for 4 weeks and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first, except specifically mentioned.

8.5 Special Considerations

- If erdafitinib needs permanent discontinuation, patients may continue fulvestrant and palbociclib treatment under study procedures
- If palbociclib needs permanent discontinuation, patients may continue fulvestrant and erdafitinib treatment under study procedures
- If both erdafitinib and palbociclib need permanent discontinuation, patients should discontinue all study drugs
- For toxicities considered (by the treating investigator) unlikely to develop into serious or life-threatening events (e.g. alopecia, dysgeusia), treatment may be continued at the same dose without reduction or interruption
- The treating investigator may reduce a subject's dose for a toxicity of any grade/duration where s/he believes it to be in the best interest of the subject
- Any consideration to alter the above dose modification guidelines should be discussed with the Protocol Chair for approval or disapproval in advance

9. DRUG FORMULATION/STORAGE/SUPPLY

9.1 Erdafitinib

Erdafitinib is an investigational agent and will be supplied free-of-charge from Janssen Research & Development.

Classification

Erdafitinib (JNJ-42756493) is an oral pan-FGFR tyrosine kinase inhibitor.

Mechanism of Action

Erdafitinib (JNJ-42756493) is a potent, oral pan-FGFR tyrosine kinase inhibitor with the biochemical inhibitory IC_{50} values <1 nM for FGFR1, <1 nM for FGFR2, 1.05 nM for FGFR3, and <1nM for FGFR4. It has demonstrated potent inhibition of cell proliferation with IC_{50} values ranging from <1 to <1000 nM in FGFR pathway-activated cancer cell lines including squamous NSCLC, gastric, breast, HCC, endometrial, bladder, multiple myeloma, and acute myeloid leukemia.

Metabolism

Erdafitinib exhibited a dose-related increase in Cmax and area under the analyte concentration-time curve (AUC) and time-independent PK within the dose range of 0.5 to 12 mg, both after single and multiple daily dosing. The actual sampling time to reach maximum concentration (tmax) ranged between 2-4 hours (erdafitinib as tablet), independent of the studied formulations. PK was characterized by moderate intersubject variability (CV% 31-39%) and low intra-subject variability (9-10%). Erdafitinib is primarily excreted in feces either as unchanged drug or as metabolites. In vitro data indicated that CYP3A and 2C9 are involved in erdafitinib metabolism. 70% and 20% of the radioactivity was recovered in feces and urine, respectively, with approximately 11% of unchanged drug recovered in urine. Erdafitinib is highly bound to plasma proteins, especially to α1-AGP (fraction unbound in oplsma being 0.36% and 0.50% in patients and healthy subjects, respectively. Apparent volume of distribution (Vd/F) of the terminal phase based on total plasma erdafitinib in healthy subjects is small (approximately 31 L), suggesting it is limited by the binding to plasma protein. Erdafitinib has low total plasma oral clearance (mean CL/F in subjects with cancer averaged 0.29 L/h; the corresponding value for healthy subjects was 0.43 L/h), likely restricted by protein binding. As a consequence, the apparent elimination half-life (t1/2) of erdafitinib is long (approximately 50 hours in healthy subjects) resulting an approximately 3- to 4-fold accumulation in Cmax and AUC following multiple daily dosing.

Precautions and Warnings

Erdafitinib is an investigational drug, with safety data available from nonclinical studies and three Phase 1 clinical studies. All subjects should be closely monitored with special attention to evidence of disturbance of phosphate homeostasis and bone pathology and ocular symptoms until sufficient clinical experience is obtained. For the most up-to-date recommendations on management of common adverse events, please refer to the protocols of ongoing clinical trials in the investigator brochure.

Contraindications

Phase 1 and 2 clinical trials with erdafitinib are still ongoing and there are currently limited data regarding the use of erdafitinib in humans, so no conclusions regarding existing contraindications can be drawn. Subjects enrolled into clinical studies with erdafitinib should adhere to specific inclusion and exclusion criteria as defined by the study protocol.

Drug-drug Interactions

Based on preliminary in vitro data, erdafitinib is metabolized by cytochrome CYP3A4 and CYP2C9. No in vivo or clinical data are available to date. For this reason, strong CYP3A4/5 and CYP2C99 inhibitors/ inducers should be used with caution; subjects should be closely monitored for potential toxicities, and appropriate action, including temporary interruption of erdafitinib, should be taken. Alternatives to concurrent administration of erdafitinib and strong or mixed CYP3A4 and CYP2C9 inhibitors (such as orally or parenterally administrated clarithromycin, ketoconazole, itraconazole, ritonavir and fluconazole) should potentially be sought, and, if no alternative treatment is available, the Study Chair should be consulted. Erdafitinib was also shown to inhibit, in *in vitro* experiments, human P-glycoprotein (P-gp), at concentrations achieved at therapeutic doses in humans. If the compound is administered with drugs that are substrates of P-gp, there is the potential for observing increased concentrations of the substrate drug. Therefore, caution should be exercised for coadministered drugs that are P-gp substrates, such as digoxin, dabigatran, apixaban, etc.

Overdosage

Dose limiting toxicities were observed at 12 mg daily and 12 mg intermittent (7 days on/7 days off), but the maximum tolerated dose was not reached.

Dosage and Administration

The clinically effective dose of erdafitinib has not yet been determined. Recommended starting dose of single agent erdafitinib is 8 mg orally once daily. This dose should be maintained and serum phosphate (PO4) level should be assessed at approximately Day 14, when the dose can be increased to 9 mg once daily in absence of severe hyperphosphatemia and significant drug-related toxicity.

Storage and handling

Tablets should be stored at room temperature, as specified at delivery and in the original packaging.

How Supplied

Detailed information on preparation, handling, and storage conditions will accompany the clinical drug supplies to the clinical study site(s). The storage conditions and expiration dates will be indicated on the label of the drug product. Erdafitinib will be supplied as 3 mg, 4 mg and 5 mg oral film coated tablets.

Disposal and destruction

The drug supply will be destroyed/ disposed of as per institutional guidelines.

9.2 Fulvestrant

Fulvestrant is commercially available and available in 50 mg/mL solution in a single use-vial for intramuscular administration.

Classification

An estrogen receptor antagonist indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

Mechanism of Action

Fulvestrant is an estrogen receptor antagonist that binds to the estrogen receptor in a competitive manner with affinity comparable to that of estradiol and downregulates the ER protein in human

breast cancer cells. In vitro studies demonstrated that fulvestrant is a reversible inhibitor of the growth of tamoxifen resistant, as well as estrogen-sensitive human breast cancer (MCF-7) cells. In *in vivo* tumor studies, fulvestrant delayed the establishment of human breast cancer MCF-7 xenografts in nude mice. Fulvestrant inhibited the growth of established MCF-7 xenografts and of tamoxifen-resistant breast xenografts. Fulvestrant showed no agonist-type effects in uterotropic assays in immature or ovariectomized mice and rats. In studies in immature rats and ovariectomized monkeys, fulvestrant blocked the uterotrophic action of estradiol. In post-menopausal women, the absence of changes in plasma concentrations of FSH and LH in response to fulvestrant treatment (250 mg monthly) suggests no peripheral steroidal effects.

Metabolism

Biotransformation and disposition of fulvestrant in humans have been determined following intramuscular and intravenous administration of 14C-labeled fulvestrant. Metabolism of fulvestrant appears to involve combinations of a number of possible biotransformation pathways analogous to those of endogenous steroids, including oxidation, aromatic hydroxylation, conjugation with glucuronic acid and/or sulphate at the 2, 3 and 17 positions of the steroid nucleus, and oxidation of the side chain sulphoxide. Identified metabolites are either less active or exhibit similar activity to fulvestrant in models of antiestrogen action. Studies using human liver preparations and recombinant human enzymes indicate that cytochrome P-450 3A4 (CYP 3A4) is the only P-450 isoenzyme involved in the oxidation of fulvestrant; however, the relative contribution of P-450 and non-P-450 routes *in vivo* is unknown.

Excretion

Fulvestrant was rapidly cleared by the hepatobiliary route with excretion primarily via the feces (approximately 90%). Renal elimination was negligible (less than 1%). After an intramuscular injection of 250 mg, the clearance (mean ± SD) was 690 ± 226 mL/min with an apparent half-life about 40 days.

Contraindications

Fulvestrant is contraindicated in pregnant women and in patients with a known hypersensitivity to the drug or to any of its components.

Drug-drug Interactions

There are no known drug-drug interactions. Although fulvestrant is metabolized by CYP 3A4 in vitro, drug interactions studies with ketoconazole or rifampin did not alter fulvestrant pharmacokinetics. Dose adjustment is not needed in patients co-prescribed CYP3A4 inhibitors or inducers.

Storage and handling

Refrigerate, 2°-8°C (36°-46°F). Protect from light, store in the original carton until time of use.

How Supplied

Commercial supplies of fulvestrant (AstraZeneca PLC) will be used in this study and billed to third party payers or to the subject. Complete and updated adverse event information is available in product package insert.

9.3 Palbociclib

Palbociclib is available in 75 mg, 100 mg and 125 mg capsules for oral administration. Palbociclib will be provided free of charge by Pfizer.

Classification

Palbociclib is a cyclin-dependent kinase (CDK) 4/6 inhibitor with antineoplastic activity indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women, in conjunction with letrozole (1st line treatment) or with fulvestrant (2nd line treatment).

Mechanism of Action

Palbociclib selectively inhibits CDK4 and CDK6, thereby dephosphorylating and inhibiting retinoblastoma (Rb) protein early in the G1 phase of the cell cycle, thus leading to suppression of DNA replication and cell cycle arrest. CDK4 and 6 are serine/threonine kinases that are upregulated in many tumor cell types and play a key role in the regulation of cell cycle progression.

Metabolism

To date, pharmacokinetic data have been collected in 4 clinical studies for a total of 138 cancer patients. The exposure and Cmax increased in a dose-proportional manner over the range of 25 to 225 mg once daily (QD) following palbociclib administration on days 1 and 8 of cycle 1, although some low to moderate variability around these doses was observed, particularly at the 150 mg QD dose level. Following repeated daily dosing to day 15 and day 21 (assumed to be steady state), palbociclib was absorbed with a median Tmax of ~4 h. The mean palbociclib Vz/F was 3103 L, which is significantly greater than total body water (42 L), indicating that palbociclib extensively penetrates into peripheral tissues. Palbociclib was eliminated slowly; the mean t½ was 26.5 h (range 15.8 to 36.2 h) and the mean CL/F was 86.1 L/h. Palbociclib accumulated following repeated dosing with a median Rac of 2.4, which is consistent with a half-life of ~27 h. Preliminary results from the recently performed food effect study (A5481021) suggested that the administration of palbociclib with food results in more consistent drug absorption and exposure than administration of palbociclib in a fasted state. As a result of these findings, patients should be instructed to take palbociclib with food. CYP3A4 inhibitors/ inducers should be avoided.

Drug-drug Interactions

The strong CYP3A inhibitor itraconazole increased palbociclib AUCinf by approximately 87%, relative to palbociclib given alone. As expected, coadministration of rifampin, a strong CYP3A inducer, decreased palbociclib AUCinf by 85% relative to palbociclib given alone. Palbociclib is a weak time-dependent inhibitor of CYP3A following administration of the clinical 125 mg dose: palbociclib increased the midazolam AUCinf values by 61%, as compared with midazolam alone. *In vitro*, palbociclib is not an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, and 2D6, and is not an inducer of CYP1A2, 2B6, 2C8, and 3A4 at clinically relevant concentrations. In vitro evaluations indicated that palbociclib has a low potential to inhibit the activities of drug transporters at clinically relevant concentrations.

Storage and handling

Palbociclib capsules should be stored at controlled room temperature (15-30°C, 59-86°F) in their original container.

Side Effects

The most frequently reported treatment-related adverse events included neutropenia, leukopenia, anemia, and fatigue. A phase II study of palbociclib showed toxicities that were mostly Grade 1 and 2; Grade 3 and 4 toxicities were limited to transient neutropenia (50%) and thrombocytopenia (21%). A large phase II study of palbociclib combined with letrozole found a 54% rate of grade 3/4 neutropenia but no increase in febrile neutropenia. Neutropenia was easily managed with dose delay and dose reduction.

How Supplied

Pfizer provides supplies of palbociclib (Pfizer) that are to be used in this study and will not be billed to third party payers or to the subject.

Disposal and destruction

The drug supply will be destroyed/ disposed of as per institutional guidelines.

9.4 Drug Accountability

Clinical drug supply must be accounted for and patients will be asked to return all unused study drug and packaging on a regular basis, at the end of the study or at the time of study drug discontinuation. Accountability for the drug at all study sites is the responsibility of the principal investigator and designated Pharmacy representative. The investigator will ensure that the investigational drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and destruction/disposal per institutional policy will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates, and patient numbers.

10. CORRELATIVE/SPECIAL STUDIES

10.1 Overview

Correlate/ Sample	Source	Local/ On-Site Processing	Central Processing	Shipping
***FGFR1* testing**	FFPE from archival tumor tissue (primary or metastatic)	Submission of FFPE archival tumor tissue block OR Submission of 5 unstained slides cut at 4 microns each placed on charged (plus) slides	Yes (*FGFR1* FISH)	Freq: Same day Temp: Ambient Lab: VUMC
	Note: Known *FGFR* amplification by FISH, NGS or cfDNA are acceptable for enrollment if previously done locally			
Next Generation Sequencing (NGS)	FFPE from archival tumor tissue (primary or metastatic)	Submission of FFPE archival tumor tissue OR Submission of: - 1 H&E (or an unstained 4 micron section on a plus [charged] slide) followed by, - 6 serial 20 micron peels placed in a DNAse-RNAse free tube (wrapped in parafilm to exclude moisture) followed by, - 1 H&E (or an unstained 4 micron section on a plus [charged] slide) - Peels should be placed in the -80 freezer upon receipt until extraction is to take place	Yes (DNA extraction for NGS)	Freq: Batched Temp: Ambient Lab: VUMC (VUMC will subsequently be responsible to batch ship to MSKCC for NGS analyses)
Whole Blood (NGS control)	Blood- 1 tube, 8 mL, PAXgene or EDTA (purple top)	-Mix by gentle inversion 8 or 10 times - Freeze and store in 20C freezer until ready to ship to MSKCC	Yes	Freq: Batched Temp: Ambient Lab: VUMC (VUMC will subsequently be responsible to batch ship to MSKCC for NGS analyses)

Note: For patients in which archival tumor is not available and a fresh tumor biopsy is obtained, the main core should be fixed for IHC analysis on site. If additional cores are collected, they can be snap-frozen and submitted as such. The invasive tumor area in the FFPE should be at least 5 mm x 5 mm and contain 20% tumor cellularity.				
cfDNA	Blood- 1 tube, 10mL, Streck	-Mix by gentle inversion 8 or 10 times -Do not refrigerate or freeze cfDNA Samples collected at VUMC only are to be pre-processed as follows: -Needed supplies: 2 x 15 ml conical tubes, 1 x 5 ml screw-cap, 3 x 5 ml pipettes -Transfer entire volume of blood from Streck tube to a 15 ml conical tube using 5 ml pipette. -Centrifuge 15 ml conical tubes at 1600xg for 10 minutes at 10˚C - Transfer supernatant to a fresh 15 ml conical tube without disturbing the cellular layer using a disposable 5 ml - Centrifuge the plasma in the second 15 ml conical tube for 3200xg for 10 minutes at 10˚C -Transfer the supernatant to 1 x 5 ml screw top tube without disturbing the cellular layer using a 5 ml pipette Leave a residual volume of about 0.3 ml (7 mm) in the bottom of the 15 ml tube to avoid cellular contamination. -Freeze supernatant at -80˚C	Yes (cfDNA analysis)	Freq: Same day Temp: Ambient Lab: VUMC
PK	Blood- 1 tube, 6 mL, Lavender-top K2EDTA vacutainer tube	- Mix by gentle inversion at least 10 times - Place tube in an ice/water bath and maintain chilled until centrifugation - Within 30 minutes of collection, centrifuge collection tubes in a refrigerated centrifuge (set to 2-8^{0}C) at a minimum of 1500 x g for 15 minutes - Use standard laboratory technique to transfer all the plasma equally into 2 appropriately labeled	Yes (PK Analysis)	Freq: Batched Temp: Frozen Lab: VUMC
PD	Blood- 1 tube, 6 mL, Lavender-top K2EDTA vacutainer tube		Yes (FGF23, sFGFR2, sFGFR3 and sFGFR4 analyses)	

		polupropylene screw-cap cryovials (one is the primary sample and the other the back-up sample) - Label cryovials accordingly - Store both plasma aliquot samples in a freezer set to maintain a temperature of -70^{0}C		
Note: PTH, Calcium, Phosphate and vitamin D will be assessed locally per institutional collection/ processing guidelines				

10.2 Blood Samples for Pharmacodynamic Assessments

Blood collection for pharmacodynamic assessments (serum phosphate, calcium, vitamin D, parathyroid hormone [PTH], FGF23, sFGFR2, sFGFR3 and sFGFR4) will be performed on Days 1 and 15 of Cycle 1 and 2 in all patients participating in the phase Ib portion of the study, to determine pharmacodynamic biomarkers of FGFR inhibition.

Serum FGFR2, FGFR3 and FGFR4 will be measured using an enzyme-linked immunosorbent assay developed at Janssen Research & Development (Raritan, NJ).

Tubes should be packed and sent according to the **Lab manual**.

If not retrieved on site by VICC CTO personnel, outside sites should ship specimens along with Tissue/Blood Registration Form directly to:

Dr. Melinda Sanders
c/o Violeta Sanchez
Vanderbilt University Medical Center
Department of Pathology 4912 TVC
1301 Medical Center Drive
Nashville, TN 37232-5310
615-343-9115

****Specimens should be mailed to arrive at VUMC from Monday 8AM through Friday 1PM****

****Specimens collected from Vanderbilt patients will be pre-processed by VICC CTO and subsequently delivered to Melinda Sanders/Violeta Sanchez for storage until processing****

10.3 Blood Samples for cfDNA

To determine if the *FGFR1* amplification levels is an early surrogate of response, and to determine if the cfDNA results at disease progression show new genomic alterations potentially associated with resistance to CDK4/6 and FGFR inhibition, blood collection for cfDNA will be performed in all patients at: **baseline** (Cycle 1 Day 1), **Day 1 of every even cycle**, and at disease progression (**end-of-treatment**). Initially, the baseline, 4-week and end-of-treatment timepoints will be submitted for cfDNA analysis; the other time points will be stored for future research.

One vial of whole blood should be collected in a Cell-Free DNA BCT tube (Streck tube). Fill the tube completely. Remove the tube from the adapter and immediately mix by gentle inversion 8 to 10 times.

Tubes should be packed according to the **Lab manual** and sent immediately (within 24 h). **Do not freeze or refrigerate specimens collected in Streck tubes as this will compromise measurements of cfDNA.**

If not retrieved on site by VICC CTO personnel, outside sites should ship specimens along with Tissue/Blood Registration Form directly to:

Dr. Melinda Sanders
c/o Violeta Sanchez
Vanderbilt University Medical Center
Department of Pathology 4912 TVC
1301 Medical Center Drive
Nashville, TN 37232-5310
615-343-9115

****Specimens should be mailed to arrive at VUMC from Monday 8AM through Friday 1PM****

****Specimens collected from Vanderbilt patients will be pre-processed by VICC CTO and subsequently delivered to Melinda Sanders/Violeta Sanchez for storage until processing****

10.4 Blood Samples for NGS control

Whole blood collection will be performed on Days 1 of Cycle 1 in all patients participating in the study, to be used as germline control once NGS analysis is done in tumor tissue.

Tubes should be packed and sent according to the **Lab manual**.

If not retrieved on site by VICC CTO personnel, outside sites should ship specimens along with Tissue/Blood Registration Form directly to:

Dr. Melinda Sanders
c/o Violeta Sanchez
Vanderbilt University Medical Center
Department of Pathology 4912 TVC
1301 Medical Center Drive
Nashville, TN 37232-5310
615-343-9115

****Specimens should be mailed to arrive at VUMC from Monday 8AM through Friday 1PM****

****Specimens collected from Vanderbilt patients will be pre-processed by VICC CTO and subsequently delivered to Melinda Sanders/Violeta Sanchez for storage until processing****

10.5 Tissue Samples

To determine the therapeutic predictive role of *FGFR1-4, CCND1-2, CDK4* and *CDK6* amplifications, and *RB1* and *ESR1* mutations on clinical outcome, FFPE tissue from primary tumor or from a metastatic tumor biopsy will be collected for *FGFR1* FISH analysis and Next Generation Sequencing in all patients enrolled in the study at the time of registration.

Collection of fresh frozen tissue from a metastasis at any point prior, during or after study drugs, is encouraged and desirable, especially in patients that achieve a good clinical response and subsequently have disease progression. The fresh biopsy will follow guidelines as listed in Section 10.4.3.

Summary of required tissue:

A) FFPE block from primary tumor or metastatic tumor biopsy, with adequate tissue to cut the tissue sections described in B) and C) below. Ideally, the invasive tumor area should be at least 5 mm x 5 mm and contain 20% tumor cellularity.

If participating institutions are not allowed to release FFPE blocks,the following should be prepared:

B) To perform *FGFR1* FISH for either pre-screening or central confirmation: 5 unstained slides cut at 4 microns each placed on charged (plus) slides. Do not bake on a hot plate (see 10.3.1).

C) To perform next generation sequencing cut in this order:

1. From a tumor block containing greater than 25 mm^2 of tumor with at least 20% tumor cellularity please provide:
    a. 1 H&E (or an unstained 4 micron section on a plus [charged] slide) followed by,
    b. 3 serial 20 micron peels placed in a DNAse-RNAse free tube (wrapped in parafilm to exclude moisture) followed by,
    c. 1 H&E (or an unstained 4 micron section on a plus [charged] slide)
    d. Peels should be placed in the -80 freezer upon receipt until extraction is to take place.

2. Tumor blocks containing 5-20 mm^2 of tumor with at least 20% tumor cellularity please provide:
    a) 1 H&E (or an unstained 4 micron section on a plus [charged] slide) followed by,
    b) 6 serial 20 micron peels placed in a DNAse-RNAse free tube (wrapped in parafilm to exclude moisture) followed by,
    c) 1 H&E (or an unstained 4 micron section on a plus [charged] slide)
    d) Peels should be placed in the -80 freezer upon receipt until extraction is to take place.

All formalin-fixed paraffin embedded tissue and/or slides should be sent with a cold pack (except in winter months) to avoid melting that could compromise tissue analysis.

****Paraffin blocks retrieved on site by VICC CTO personnel along with Tissue/Blood Registration Form should be delivered directly to the persons below who will prepare the samples listed above:**

Dr. Melinda Sanders
c/o Violeta Sanchez
Vanderbilt University Medical Center
Department of Pathology
4912 TVC 1301 Medical Center Drive
Nashville, TN 37232-5310
615-343-9115

****Paraffin blocks, slides and tissue peels from outside sites should ship specimens along with Tissue/Blood Registration Form directly to:**

Dr. Melinda Sanders
c/o Violeta Sanchez
Vanderbilt University Medical Center
Department of Pathology

4912 TVC 1301 Medical Center Drive
Nashville, TN 37232-5310
615-343-9115

10.5.1 *FGFR1* Fluorescence *In Situ* Hybridization (FISH)

Patients with known (i.e. local determination of) *FGFR1-4* amplification (by NGS, cfDNA or FISH) are eligible for study participation. For patients with FGFR1 amplification, central confirmation of *FGFR1* amplification by FISH will be performed, but will not be required for study treatment initiation. Patients without known *FGFR1* amplification can send tissue for *FGFR1* amplification screening via FISH analysis at the Vanderbilt-Ingram Cancer Center (VICC) in the CLIA-certified Vanderbilt University Medical Center Cytogenetics Laboratory. Patients with known *FGFR2-4* amplifications (by local determination of NGS, cfDNA or FISH) will not have central confirmation of amplification status by FISH due to their overall low prevalence. From the time tissue arrives at the Coordinating Center Breast Cancer Tissue Core (Dr. Melinda Sanders), a turn-around time of no longer than 7 days should be expected for the FISH results to become available thus determining if a patient is eligible or not.

FGFR1 FISH will be performed as follows: three to four-µm tissue sections will be mounted on sialinized slides and hybridized overnight with the Zyto*Light* SPEC *FGFR1*/CEN 8 Dual Color Probe (ZytoVision, Bremerhaven, Germany). Briefly, after deparaffinization, the slides are denatured in the presence of 10 µl probe for 6 min at 73°C and hybridized at 37°C overnight in StatSpin (Thermobrite, Abbott Molecular, Inc.). Post-hybridization SSC washes are performed at 72°C and then the slides are stained with DAPI before analysis. Slides are analyzed with Reflected light fluorescent microscope (Olympus BX60) at 100X for hot spots. Representative images of tumor cells are captured using Cytovision software. Thirty tumor cell nuclei from hot spots or random areas are individually evaluated with the Olympus BX60 at 100X by counting green *FGFR1* and orange centromer 8 (CEN8) signals. The average of *FGFR1* copy number and the *FGFR1*/CEN8 is then calculated. Tumors are considered as *FGFR1* positive ('amplified') under one of the following conditions:

- The *FGFR1*/CEN8 ratio is ≥2.0;
- The average number of *FGFR1* signals per tumor cell nucleus is ≥6[40].

10.5.2 Next Generation Sequencing

DNA will be extracted using DNEasy or QiaAMP DNA tissue kits from FFPE archival tumor sections or snap-frozen biopsies of metastases, respectively. Tumor cellularity is assessed by an expert breast pathologist (MES); specimens with ≥ 20% tumor nuclei are considered evaluable. In the few cases with paucicellular samples (< 20% tumor cells), multiple sections were macro-dissected to achieve ≥ 20% tumor cellularity.

Subsequently, Next Generation Sequencing (NGS) will be performed using the MSK-IMPACT™ (Memorial Sloan Kettering - Integrated Mutation Profiling of Actionable Cancer Targets)[46], a hybridization capture-based assay for targeted deep sequencing of all exons and selected introns of 341 key cancer genes in DNA from FFPE tumor sections. Custom DNA probes targeting exons and selected introns of 341 genes are synthesized using the NimbleGen SeqCap EZ library custom oligo system and biotinylated to allow for sequence enrichment by capture using streptavidin-conjugated beads. Pooled libraries containing captured DNA fragments are subsequently sequenced on the Illumina HiSeq 2500 system (rapid-run mode) as 2 × 100-bp paired-end reads.

10.5.3 Guidelines for Tissue Acquisition on Biopsies of Metastatic Lesions (when applicable)

Tissue specimens, when feasible, will be collected from recurrent or metastatic lesions using standard institutional procedures. The amount of tissue collected will follow the guidelines listed below. If a patient has more than one site of disease, only one site needs to be biopsied, and the site is left to the discretion of the patient and her treating physician. If a patient is undergoing resection of a lesion for clinical reasons (i.e. wedge resection of a new lung lesion for confirmation of diagnosis or re-testing of hormone receptor and/or HER2 status, or, resection of a chest wall lesion, or, resection of a lymph node), then the patient may opt to have a portion of that tissue (roughly equivalent to the goal amount of tissue listed in the guidelines above, i.e. the equivalent of two 5-mm punch biopsies of the skin, or 3-6 18-gauge core biopsies) stored for research at the time of the procedure.

Core biopsies are always preferred over fine needle aspirates when both are technically feasible and safe. Fine needle aspirates (FNA) are acceptable and may be used for the baseline tissue sample but may not provide enough or adequate DNA for NGS.

Listed below are the goal amounts of tissue for patients who undergo core biopsy or punch biopsy, or who have either ascites fluid or pleural fluid accessible for collection. Please note that the guidelines below are for the amount of tissue to be obtained at the baseline biopsy, and are not meant to replace clinical judgment at the time the procedure is performed. Less than the goal quantity of tissue is accepted for each type of biopsy, and will be left to the clinical judgment of the physician performing the procedure.

- Breast: A goal of 3-6 core biopsy specimens will be obtained using standard institutional guidelines for a diagnostic core biopsy of a breast mass
- Skin/chest wall: A goal of one to two 5-mm punch biops(ies)
- Lymph node: A goal of 3-6 core biopsy specimens will be obtained using an 18-gauge needle
- Liver: A goal of 3-6 core biopsy specimens will be obtained using an 18-gauge needle
- Lung: Because of the risk of pneumothorax associated with core needle biopsies of lung nodules, no core biopsies of lung nodules will be performed on this protocol
- Bone: Because the yield of malignant tissue from bone biopsies tends to be relatively low, if a patient has another accessible site of disease (i.e. skin, lymph node, liver), that site should be biopsied preferentially. If bone is the only biopsy-accessible site, then a goal of 3-6 core biopsy specimens will be obtained using an 18-gauge needle. It is critical that every attempt be made to process a portion of the specimen without decalcification or decalcification with EDTA instead of Formic acid as the mutational analysis cannot be performed on decalcified specimens.
- Pleural Fluid: A goal of 500 mL of pleural fluid will be obtained with a standard thoracentesis procedure, with or without image guidance, according to the clinical judgment of the treating physician and clinician performing the procedure. Less than the goal amount is acceptable, and should be based upon the clinical judgment of the Investigator and the clinician performing the procedure. If more than the goal amount of fluid is obtained, then the entire specimen (with the exception of what is needed for clinical purposes, if applicable) will be stored in the tissue bank.
- Ascites fluid: A goal of 500 mL of ascites fluid will be obtained with a standard paracentesis procedure, with or without image guidance, according to the clinical judgment of the treating physician and clinician performing the procedure. Less than the goal amount is acceptable,

and should be based upon the clinical judgment of the Investigator and the clinician performing the procedure. If more than the goal amount of fluid is obtained, then the entire specimen (with the exception of what is needed for clinical purposes, if applicable) will be stored in the tissue bank.

- For patients in whom a core biopsy is not possible and who thus undergo FNA, 3 passes should be collected.

10.5.4 Instructions on fresh tissue specimen handling

If feasible, at least four core biopsy specimens should be obtained:

- Two core biopsy specimens should be snap-frozen in liquid nitrogen
- Two core biopsies should be suspended in freshly prepared 10% buffered formalin
- If additional core biopsies are obtained, 1-2 cores should be snap-frozen
- If only 1 core biopsy is obtained, it should be snap-frozen in liquid nitrogen
- If only 2 core biopsies are obtained, one should be snap-frozen in liquid nitrogen and the other should be suspended in freshly prepared 10% buffered formalin
- Do not put tissue into any solution.

For patients in whom a core biopsy is not feasible and who thus undergo FNA:

- 3 passes should be collected
- All passes should be evacuated and rinsed directly into 10% buffered formalin in the same container

10.5.5 Tissue specimen labeling and documentation

- Label ALL specimens before freezing
- If sample comes in contact with contaminate, make note in information section of paperwork.
- Enter time core biopsy was collected on paperwork.
- Label each collection containers with Patient ID sequence number/code letter, Medical Record #, site and location of biopsy, date and time.
- If not retrieved on site by VICC CTO personnel, outside sites should ship specimens along with Tissue/Blood Registration Form directly to:

Dr. Melinda Sanders
c/o Violeta Sanchez
Vanderbilt University Medical Center
Department of Pathology, 4912 TVC
1301 Medical Center Drive
Nashville, TN 37232-5310
615-343-9115

The specimens will be logged in as a consented specimen and either be stored frozen or as paraffin-embedded tissue and available for molecular pathology studies. **Ship ALL frozen samples packed with dry ice.**

****Specimens should be mailed to arrive at VUMC from Monday 8AM through Friday 1PM****

10.6 Pharmacokinetics

Full pharmacokinetic (PK) sampling of erdafitinib and palbociclib in combination with fulvestrant will be performed on Days 1 and 15 of Cycles 1 and 2 in all patients participating in the phase Ib

dose escalation portion of the trial treated on the daily dosing schedule. Of note, PK samples could be obtained from additional patients if there are concerns about the PK profiling and/or clinical safety based on the available results.

The collection time of all samples must be documented in the PK Blood Collection eCRF pages. The exact time of oral erdafitinib dosing, date sample was taken and actual time of sampling must be entered on the eCRF. Any sampling problems (e.g., patient took study drug before a pre-dose sample) must be noted in the comments section of the eCRF. On days and time-points when blood samples for biomarkers and pharmacokinetics are to be performed, the pharmacokinetic sample must be drawn first. A meal record, if feasible, should be completed on the eCRF on days of PK assessment.

On the days of full pharmacokinetic sampling, patients should take their medication at the clinic. Patients who forget to postpone their dose on these days and take their medication at home will be excluded from pharmacokinetic blood sampling for that day and they should not have blood samples collected. On the days of full pharmacokinetic sampling, the exact time of any episodes of vomiting within the first 24 h post-dosing on that day must be noted in a separate section of the eCRF. Similarly, in case of any increase of stool frequency (i.e. diarrhea) within the first 24 h post-dosing on that day, this should also be documented in a separate section of the eCRF.

The days of full pharmacokinetic blood sampling should be representative of the other study days with regard to the use of the chronically administered concomitant medications. Therefore, patients taking medication chronically should be maintained on the same dose and dose schedule throughout the study period, as medically feasible. An intermittent concomitant medication should be avoided on the days of full pharmacokinetic sampling.

All pharmacokinetic blood samples will be taken by either direct venipuncture, an indwelling cannula inserted in a forearm vein, or via a port-a cath. Please refer to the **Lab Manual** for detailed instructions for the collection (including sampling schedule if an alternative dosing schedule is adopted), handling, and shipping of samples.

The sampling regimen assumes that both erdafitinib and palbociclib will be swallowed concomitantly, or less than 5 minutes apart, and that both drugs will be taken at the same time every day. When patients come for the pre-dose PK (except for Cycle 1, Day 1), the time when erdafitinib and palbociclib were taken the day before should be noted. The blood sampling regimen for determining the pharmacokinetics of erdafitinib and palbociclib is given in Table 10.5.1 and 10.5.2. If the evaluation of emerging data of erdafitinib indicates that it may be desirable to explore different doses or schedules of erdafitinib, then new cohorts of patients will be enrolled. A dosing schedule modification would be based on PK, PD and/or safety assessments. The collection time of all samples must be documented in the PK Blood Collection.

Table 10.5.1: PK blood collection plan daily dosing schedule

PK blood draws		Cycle 1		Cycle 2	
		Day 1	Day 15	Day 1	Day 15
Pre-dose		X	X	X	X
Post-dose	1h ± 15 min	X	X	X	
	2h ± 15 min	X	X	X	
	4h ± 15 min	X	X	X	

	8h ± 1 hour	**X**	**X**	**X**	

Table 10.5.2: PK Sample Numbers Labeling

Cycle	Day	Time (hr.)	Sample number	Description
1	Day 1	0	US101	Pre-erdafitinib and palbociclib dose
1	Day 1	1h	US103	1h post-erdafitinib and palbociclib dose
1	Day 1	2h	US104	2h post-erdafitinib and palbociclib dose
1	Day 1	4h	US106	4h post-erdafitinib and palbociclib dose
1	Day 1	8h	US107	8h post-erdafitinib and palbociclib dose
1	Day 15	0	US108	Pre-erdafitinib and palbociclib dose
1	Day 15	1h	US110	1h post-erdafitinib and palbociclib dose
1	Day 15	2h	US111	2h post-erdafitinib and palbociclib dose
1	Day 15	4h	US113	4h post-erdafitinib and palbociclib dose
1	Day 15	8h	US114	8h post-erdafitinib and palbociclib dose
2	Day 1	0	US115	Pre-erdafitinib and palbociclib dose
2	Day 1	1h	US117	1h post-erdafitinib and palbociclib dose
2	Day 1	2h	US118	2h post-erdafitinib and palbociclib dose
2	Day 1	4h	US120	4h post-erdafitinib and palbociclib dose
2	Day 1	8h	US121	8h post-erdafitinib and palbociclib dose
2	Day 15	0	US122	Pre-erdafitinib and palbociclib dose

10.6.1 Analytical method

Erdafitinib concentrations in plasma will be determined by a validated bioanalytical method with an anticipated lower limit of quantification (LLOQ) of approximately 1 ng/mL which may be improved according to eventual needs for a higher sensitivity. In addition to erdafitinib analysis, exploratory erdafitinib metabolite analysis on remaining plasma material may be performed using a non-validated, semi-quantitative or qualitative LCMS/MS method, if deemed appropriate.

10.7 Genetic Testing

Participants will be given information as part of the informed consent process that samples will be used for research tests that will include genetic studies and testing. The intent is not to give participants (or his/her medical providers) the results of any testing done for research purposes; however, incidental germline (heritable) mutations may be identified of which a participant may or may not already be aware. In the case that an incidental genetic finding is identified, the Protocol Chair of this project will be notified. The possible decisions for handling incidental findings may include notification of the participant (and provider); recommendation for genetic counseling, which may or may not include genetic testing (e.g., if the finding was not done in a CLIA certified laboratory); or, neither. In general, a member of the participant's treating team will be given the information to help with notification. In all cases, the current policy of the Vanderbilt-Ingram Cancer Center and local/participating site IRB, as applicable, will be followed and any additional approvals that may be required prior to participant notification will be secured in advance.

11. SPECIMEN BANKING

The study Protocol Chair and collaborators have approval by the TBCRC to use all research bio-specimens collected during the conduct of this trial to address the research questions described in the protocol document. All future use of residual or repository specimens collected in this trial for purposes not prospectively defined will require review and approval by the TBCRC according to its established policies, whether the specimens are stored in a central site or at a local institution in a virtual repository. Secondary use of biospecimens for new endpoints must be submitted to the TBCRC Central Office for possible review by the TBCRC Correlative Science Review Committee.

12. MEASUREMENT OF EFFECT

For the purposes of this study, patients should be re-evaluated for response after every 2 cycles. Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) Committee (version 1.1)[47]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

12.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first administration of study treatment drugs.

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

12.2 Disease Parameters

12.2.1 Measurable

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

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

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

12.2.2 Non-measurable

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

12.2.3 Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

12.2.3.1 Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above
- Blastic bone lesions are non-measurable

12.2.3.2 Cystic lesions:

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

13.2.3.3 Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless disease progression there has been demonstrated

12.2.4 Specifications by methods of measurements

12.2.4.1 Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

12.2.4.2 Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but is/are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. Guidelines have defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilisation of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalise for a patient to be considered in complete response.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with taxanes or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered, if measurable lesions have met criteria for response or stable disease, in order to differentiate between response (or stable disease) and progressive disease.

12.3 Response Criteria

12.3.1 Target lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as **target lesions** and will be recorded and measured at baseline. This means that in instances where patients have only one or two organ sites involved, a maximum of two and four lesions, respectively, will be recorded.

12.3.2 Evaluation of Target Lesions

12.3.2.1 Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

12.3.2.2 Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

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

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

to qualify for PD, taking as reference the smallest sum of diameters while on study.

12.3.3 Non-target lesions:

All other lesions (or sites of disease) including pathological lymph nodes should be identified as **non-target lesions** and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or, in rare cases 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

12.3.4 Evaluation of Non-Target Lesions

12.3.4.1 Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be non-pathological in size (<10 mm in their short axis).

12.3.4.2 Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker levels above the normal limits.

12.3.4.3 Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

12.3.5 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocol must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one as the 'best overall response'.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	Not evaluated	No	PR
PR	Non PD or not all evaluated	No	PR
SD	Non PD or not all evaluated	No	SD
Not all evaluated	Non PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR=complete response, PR=partial response, PD=progressive disease, SD=stable disease, NE=not evaluable.

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. In these patients, every effort should be made to document the objective progression even after discontinuation of treatment.

12.4 Duration of Response

12.4.1 Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

12.4.2 Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

13. ADVERSE EVENT REPORTING REQUIREMENTS

13.1 General

Adverse event collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) that is available at http://ctep.cancer.gov/reporting//ctc.html.

Information on all adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.

Adverse events, special situations including pregnancies and product quality complaints experienced by participants will be collected and reported from initiation of study-related procedures (i.e from time of consent form signature), throughout the study, and within 30 days of the last documented dose of study medication. Participants who experience an ongoing adverse event related to a study procedure and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator.

For the purposes of this study, the J&J medicinal product is: Balversa (Erdafitinib (JNJ-42756493)
Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study drugs.

13.2 Definitions

13.2.1 Adverse Event (AE)

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can

therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

13.2.2 Serious adverse event (SAE)

A serious adverse event is an undesirable sign, symptom or medical condition which:

- is fatal or life-threatening (the subject was at risk at the time of the event. It does not refer to an event that hypothetically may have caused death if it were more severe);
- requires or prolongs inpatient hospitalization;
- results in persistent or significant disability/incapacity;
- constitutes a congenital anomaly or birth defect; or
- is a suspected transmission of any infectious agent fia a medicinal product
- jeopardizes the participant and requires medical or surgical intervention to prevent one of the outcomes listed above.
- is medically important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

13.2.3 Expectedness

- Expected: Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.
- Unexpected: An adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk

13.2.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment
- Probable – The AE is likely related to the study treatment
- Possible – The AE may be related to the study treatment
- Unlikely - The AE is doubtfully related to the study treatment
- Unrelated - The AE is clearly NOT related to the study treatment

13.3 Reporting Procedures

13.3.1 General Considerations

All adverse events will be captured on a centralized electronic case report form called ON-line Clinical Oncology Research Environment = Oncore

(http://www.vicc.org/ct/research/oncore.php).

Oncore is a highly secure, web based, cancer specific, and customizable system that provides fully integrative clinical data management and study administration capabilities developed in an ongoing collaborative effort with NCI designated Comprehensive Cancer Centers. It fully integrates study administration functionality including protocol tracking, patient registration, NCI reporting, review committee tracking, and SAE tracking, with clinical data management functionality including electronic case report forms (eCRF) design, clinical data capture, protocol and regulatory compliance monitoring. Specified members at each TBCRC participating site will submit all regulatory documents to the Coordinating Center Data Manager, who will upload them on Oncore.

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs, and avoid colloquialisms and abbreviations. If known at the time of reporting, a diagnosis should be reported 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, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death." Deaths that occur during the protocol specified adverse event reporting period that are attributed by the investigator solely to progression of disease should be recorded only in the study eCRF.

NOTE: Death for any reason should be reported as a Serious Adverse event.

The cause of death of a subject in a study within 30 days of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A pre-existing medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or

character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing conditions; or
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study; or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study; or
- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility); or
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]

13.3.2 Serious Adverse Events

All serious adverse events, regardless of causality to study drug, will be reported to the Principal Investigator and/or the Study Coordinator at each institution, and also to the Coordinating Center.

All serious adverse events must be reported to the Coordinating Center within 24 hours of the site becoming aware of the event. Sites will email or fax the SAE forms to the cooridinating center at: **coordinating.center@vvumc.org**. The coordinating center will report SAEs to the FDA via MedWatch form (3500).

ATTN: VICC CTO Personnel
EMAIL: Coordinating.center@vumc.org
FAX: (615) 875-0040

Follow-up information must also be reported within 1 business day of receipt of the information by the investigator.

The Coordinating Center will disseminate information regarding serious adverse events to the participating sites within 5 days of review of the information by the Protocol Chair (or her designee in the event of extended absence) only in the case that the event(s) is/are believed to be related (i.e., possibly, probably or definitely) to the study medication. The Coordinating Center will be responsible for reporting of events to the FDA and supporters, as appropriate (outlined below).

13.3.3 Adverse Events of Special Interest

For erdafitinib, adverse events of special interest include:

- Central Serous Retinopathy: including PTs of retinal detachment, chorioretinopathy, detachment of retinal pigment epithelium, retinopathy, vitreous detachment, retinal edema, detachment of macular retinal pigment epithelium

13.3.4 Institutional Review Board

All adverse events and serious adverse events will be reported to the IRB per current institutional standards. If an adverse event requires modification of the informed consent, these modifications will be provided to the IRB with the report of the adverse event. If an adverse event requires modification of the study protocol, these modifications will be provided to the IRB as soon as is possible.

13.3.5 Food and Drug Administration (FDA)

In this trial, unexpected adverse events believed to be definitely, probably, or possibly related to the medications will be reported to the FDA via MedWatch (using the online form available at https://www.accessdata.fda.gov/scripts/medwatch/; by telephone 1-800-FDA-1088; or by fax 1-800-FDA-0178 using form available at http://www.fda.gov/medwatch/report/hcp.htm). The Coordinating Center will be responsible for correspondence regarding adverse events with the FDA for all participating sites.

13.3.6 Pfizer, Inc.

The Coordinating Center will receive information from participating sites of all SAEs and other reportable events, and will report to Pfizer as detailed below:

- If an SAE occurs, Pfizer is to be notified within 24 hours of coordinator center awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding and occupational exposure cases.
- In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (e.g., if an outpatient study patient initially seeks treatment elsewhere), the coordinating center is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.
- For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on non-SAEs. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

13.3.7 Janssen Research & Development

The Coordinating Center will report any safety information that meets the criteria noted to Janssen on a Serious Event Report Form within 24 hours of the coordinating center becoming aware of the event

All adverse events, adverse events of interest (section 13.3.3), product quality complaints and safety events of interest (including pregnancy) (listed below) whether serious or non-serious, related or not related, following initiation of study procedures (i.e. from time of informed consent signature) are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a J&J medicinal product.

All (serious and non-serious) adverse events reported for a J&J medicinal product should be followed-up in accordance with clinical practice.

Safety events of interest for a J&J medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a J&J medicinal product
- Exposure to a J&J medicinal product from breastfeeding
- Suspected abuse/misuse of a J&J medicinal product
- Inadvertent or accidental exposure to a J&J medicinal product
- Medication error, intercepted medication error or potential medication error involving a J&J medicinal product (with or without patient exposure to the J&J medicinal product(s) under study, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product
- Unexpected thereapeutic or clinical benefit from use of a J&J medicinal product
- Any failure of expected pharmacological action (i.e. lack of effect of a K&J medicinal product

These safety events may not meet the definition of an adverse event; however, from Janssen's perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to Janssen within 24 hours of the coordinating center becoming aware of the event.

Individual Case Safety Report (ICSR)

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)

- an identifiable reporter (investigational site)
- a J&J medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected J&J medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- J&J protocol ID

Pregnancy

All initial reports of pregnancy must be reported to the the Coordinating Center **within 24 hours of becoming aware of the event** using the Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported.

Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the J&J medicinal product may have an effect on sperm, pregnancies in partners of male subjects exposed to a J&J medicinal product will be reported to Janssen within w**ithin 24 hours of Coordinating Center knowledge of the event** using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required

Safety Data and Product Quality Complaints (PQCs) for Janssen Medicinal Products

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

PQC Reporting

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, J&J and are mandated by regulatory agencies worldwide. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a J&J medicinal product under study must be reported to **to Janssen within within 24 hours of** Coordinating Center being made aware of the event.

If the defect for a J&J medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the PQC must reported to Janssen by the the Coordinating Center according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested.

All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to a J&J medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a J&J medicinal product.

All (serious and non-serious) adverse events reported for a J&J medicinal product should be followed-up in accordance with clinical practice.

AE Reports (Incoming) **Single Case AE/SAE Reports should be sent via SecureEmail to Janssen**:

- Enter the following web address into your web browser (personnel need to have been registered with Cisco AND have their email/password): https://res.cisco.com/websafe/root
- In the "To" box, enter IIS-BIO-VIRO-GCO@its.jnj.com

14. DATA AND SAFETY MONITORING

14.1 Data Management and Reporting

Data will be collected using a centralized electronic case report form called **ON**-line **C**linical **O**ncology **R**esearch **E**nvironment (Oncore), located at

< **http://www.vicc.org/ct/research/oncore.php** >.

Oncore is a highly secure, web based, cancer specific, and customizable system that provides fully integrative clinical data management and study administration capabilities developed in an ongoing collaborative effort with NCI designated Comprehensive Cancer Centers. The system is capable of storing basic protocol information (e.g. IRB approval dates, dates for annual renewals) and clinical trials research data. It fully integrates study administration functionality including protocol tracking, patient registration, NCI reporting, review committee tracking, and SAE tracking with clinical data management functionality including electronic case report forms (eCRF) design, clinical data capture, protocol and regulatory compliance monitoring.

Oncore allows the investigator to define specific protocol requirements and generate data collection forms. Creation of the data collection form is done with a single button click after the parameters of an individual protocol have been specified. Oncore also permits specification of study protocols, management of patient enrollment, clinical data entry and viewing, and the generation of patient or study-specific reports based on time stamping. OnCore is embedded with a comprehensive domain repository of standard reference codes and forms to promote standardization. The sources for the repository include CDUS, CTC, CDEs from NCI, ICD, MedDRA and various best practices from contributing NCI-designated Comprehensive Cancer Centers. OnCore provides several reporting features specifically addressing NCI Summary 3 and Summary 4 and other reporting requirements. Data may also be exported in a format suitable for import into other database, spreadsheets or analysis systems (such as SPSS). This system will be used to manage all VICCC clinical trials data. OnCore is maintained and supported in the VICC Clinical and Research Informatics Resource.

Specified site members will submit all pertinent regulatory documents to the Coordinating Center Data Manager, who will store it in a secure location.

The Principal Investigator or designee will inform Janssen Research & Development as defined in established Safety and Data Exchange Agreement (SDEA) of any serious adverse event, and will inform the Vanderbilt IRB in accordance with IRB policy. The Principle Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as specified in this protocol. Whenever there is a safety evaluation during the study, the treating investigator or site staff will be responsible for detecting, documenting and reporting AEs and SAEs, as detailed in the protocol. If any problem is identified related to the conduct of this research, the VICC Data Safety and Monitoring Committee (DSMC) will be formally asked to review the study and the situation that required DSMC intervention.

14.2 Data Handling and Record Keeping

An electronic case report form (Oncore eCRF) is required and must be completed for each included participant.

The investigator or designee may maintain records separate from the case report forms in the forms of clinic charts, medical records, original laboratory, radiology and pathology reports, pharmacy records, etc. The investigator will document in the clinic chart or medical record the date on which the patient signed informed consent prior to the patient's participation in the trial. Source documents must completely reflect the nature and extent of the patient's medical care, and must be available for source document verification against entries in the case report forms. Source documents regarding procedures such as scans and laboratory evaluations performed as part of the standard of care prior to enrollment in the study can be used to fulfill certain screening and baseline assessments. All information obtained from source documents will be kept in strict confidentiality. Source data sent as supporting documentation to regulatory authorities for serious adverse events will be de-identified to preserve confidentiality.

To enable evaluations and/or audits from Health Authorities and Vanderbilt the investigator agrees to keep records including: The identity of all participants (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. To comply with international regulations, the records should be retained by the investigator in compliance with regulations.

During data entry, range and missing data checks will be performed online. The checks to be performed will be documented in the Data Monitoring Plan for the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRF's will

be generated and transmitted to the site and the site monitor. Corrections will be made by the study site personnel. This will be done on an ongoing basis.

14.3 Meetings

This trial will be monitored by the VICC Breast Cancer Research Team. The Breast Cancer Research Team is composed of the Clinical Core Director of the Breast Cancer Program and Team Leader, surgical oncologists, radiation oncologists, medical oncologists, research nurses, data managers, and our regulatory specialist. The Breast Cancer Research Team meets *informally* weekly and *officially* on a monthly basis to discuss all AEs/SAEs, accrual, compliance, safety issues, adherence to protocol, data reviews, etc. pertaining to all breast cancer clinical trials. This particular study will be thoroughly reviewed during these meetings. The monthly meetings have minutes recorded each time, those are also reviewed on a monthly basis by the Breast Cancer Research Team Physician Leader.

Teleconferences between TBCRC participants and the Breast Cancer research team at Vanderbilt will be held every other week during escalation phase and monthly during expansion phase, to discuss all issues related to the trial (AEs/SAEs, accrual, compliance, safety issues, adherence to protocol, data reviews, etc.).

14.4 Monitoring

The Vanderbilt-Ingram Cancer Center (VICC) oversees patient safety and data monitoring for its investigator-initiated and NIH-NCI funded clinical trials through its Data and Safety Monitoring Committee (DSMC). The purpose of the DSMC is to ensure the efficient implementation and management of VICC Data and Safety Monitoring Plan (DSMP). The Committee maintains authority to intervene in the conduct of studies as necessary to ensure clinical research performed at VICC achieves the highest quality standards.

The VICC DSMC meets on a quarterly basis and ad hoc to discuss data and safety monitoring of clinical trials and to oversee the VICC DSMP. Internal audits for compliance with adverse event reporting, regulatory and study requirements, and data accuracy and completion are conducted according to the VICC DSMP according to study phase and risk. The committee reviews all serious adverse events (SAE) on Vanderbilt sponsored investigator-initiated studies on a quarterly basis and provides DSMC SAE review reports to the Vanderbilt IRB.

The investigator will allow the VICC-DSMC designee access to all pertinent medical records, as required by federal regulations, in order to allow for the verification of data gathered in the electronic data case report forms (eCRFs) and for the review of the data collection process. The VICC-DSMC designee will review various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and with the principles of Good Clinical Practice; completion of case report forms; source data verification; study drug accountability and storage; facilities and staff. The investigator and the investigational site staff must be available to meet with the VICC-DSMC designee in order to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the monitor.

In addition to the above, the FDA may review the conduct or results of the study at the investigational site.

In accordance with HIPAA and associated privacy regulations, a subject's authorization to use personally identifiable health information may be required from each subject before commencement of research activities. This authorization document must clearly specify what

parties will have access to a subject's personal health information, for what purpose and for what duration.

The trial additionally will be monitored by the VICC Multi-Institutional Coordinating Center. The actual frequency of monitoring will depend on the enrollment rate and performance of the site. Monitoring will be conducted through onsite and/or remote monitoring, teleconferences with the Investigator and site staff, and appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure that the study is conducted in compliance with the protocol, standard operating procedures (SOPs), and other written instructions, and to ensure the quality and integrity of the data.

During scheduled monitoring visits, investigators and the investigational site staff must be available to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests, provide required regulatory documents, and respond to any other trial-related inquiries of the monitor.

In addition to the above, the FDA may review the conduct or results of the study at the investigational site.

15. REGULATORY CONSIDERATIONS

15.1 Pre-Study Documentation

Each participating site is responsible for submitting copies of all relevant regulatory documentation to the Coordinating Center. The Coordinating Center will provide each participating site with a comprehensive list of the necessary documents. It is the responsibility of the participating sites to maintain copies of all documentation submitted to the Coordinating Center.

The required documents include but are not limited to the following:

- A signed FDA Form 1572
- A current *curriculum vitae* and medical license of the Principal Investigator and each sub-investigator listed on the FDA Form 1572
- A letter from the IRB stipulating approval of the protocol, the informed consent document and any other material provided to potential trial participants with information about the trial (e.g. advertisements)
- A copy of the IRB-approved informed consent document
- The current IRB membership list for the reviewing IRB
- A completed financial disclosure form for the investigator and all sub- investigators
- Current laboratory certification for the reference laboratory and *curriculum vitae* of the laboratory director
- A list of current laboratory normal values for the reference laboratory

The requirements for data management, submissions, and monitoring are outlined below. The participating sites will submit all the research related information inclusive of:

- Source documents (patient registration list, CRF info, toxicity assessments, tumor measurements / responses, etc.) are required to be provided within 30 days of visit or 10 days in advance of a monitoring visit or audit,
- Essential Documents (IRB approval documents, financial disclosure forms, 1572, delegation of authority log, protocol training, etc.) are required to be provided within one week of receiving the updated documents.

Personnel from the VICC Clinical Trials Office will monitor the trial and may periodically visit the investigative site to assure proper conduct of the trial and proper collection of the data. The investigators at other sites will allow the monitor to review all source documents used in the preparation of the case reports.

15.2 Protocol Review and Amendments

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per the current institutional standards of each participating center. Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB of each institution prior to implementation.

The Protocol Chair (or designee) is responsible for the coordination and development of all protocol amendments, and will disseminate this information to the participating centers.

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review

Board/Independent Ethics Committee (IRB/IEC/REB). Any amendments to the protocol, other than administrative ones, must be approved by this committee.

Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB/IEC/REB. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC/REB approval but the IRB/IEC/REB of each center must be kept informed of such administrative changes.

15.3 Informed Consent

The investigator (or his/her designee) will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary, that s/he may withdraw from the study at any time, and that withdrawal of consent will not affect her subsequent medical treatment or relationship with the treating physician(s) or institution. The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved. The subject should read and consider the statement before signing and dating it, and will be given a copy of the document. No subject will enter the study or have study-specific procedures done before his/her informed consent has been obtained.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the Coordinating Center and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

15.4 Confidentiality and Disclosure

The investigator agrees to keep all information provided by this study in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided (protocols, investigators' brochures, CRFs and other material) will be stored appropriately to ensure their confidentiality.

Patient medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited. Upon the patient's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. This medical information must be made available to the IRB and DSMC, upon request, for source verification of study documentation. Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA, local health authorities, Dr. Vandana Abramson and her authorized representative(s), collaborators and licensees, and the IRB for each study site, if appropriate. We will make all reasonable efforts to keep patient's protected health information (**PHI**) private and confidential. We will only utilize or relinquish this kind of information according to federal privacy guidelines. There are many safeguards in place to prevent the unintentional disclosure of information obtained for or produced by this study. Research data, including the data collected from the medical charts will be entered into a password-protected database. Any publications or public disclosure of data relating to the patient's tumor will be done without any identifying information.

PHI will be collected and stored in the ONCORE research database. The coordinating center will have access to all research data, which will be kept for at least 2 years after the study is

completed. Any research data entered in a patient medical record will be stored for an indefinite amount of time. There are no plans to destroy data at this time.

Confidentiality and security will be maintained for the tissue collection within this study. All tissue samples obtained for this study will be assigned a code and this code used to identify the sample. The samples will not be labeled with the patient's name, address or other information that would identify them. All information will be coded to maintain privacy. Research data, including the data collected from the medical charts will be entered into a password-protected database. The database (Breast Cancer Program Database) in which this study data are going to be stored has a firewall (in addition to the institutional firewall) with the highest level of protection, i.e. the same level of protection as the on-line hospital information system at Vanderbilt. This means that users must log on to a web server that sits between the institutional firewall and the firewall to the database, and only this application server is allowed to query the database. Information, including the identifier and password for the authorized users, is transmitted via a secure shell protocol using 128k encryption. Only Dr. Vandana Abramson, the PI, and the Breast Team Data Manager, approved through our IRB will be allowed access to patient identifiers. Other levels of authorization may exist for approved users, e.g. access to de-identified data. This database will store a de-identified link to the patient data and will not otherwise store patient data, even de-identified data. The safety monitoring will be performed by the groups deemed appropriate by the Vanderbilt University Medical Center IRB for reviewing the clinical trials procedure. Safety monitoring for the database is also performed by the Networking and Security Services of the Vanderbilt University Medical Center. Audit trails for access to the web server and the databases behind the dual firewall system are maintained in accordance with the practices of the Networking and Security Services of the Vanderbilt University Medical Center.

The investigator agrees to keep all information provided by Janssen Research & Development in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by Janssen Research & Development (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided by Janssen Research & Development to the investigator may not be disclosed to others without direct written authorization from Janssen Research & Development, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

15.5 Records Retention

The investigator will retain the records of the clinical trial (including, but not necessarily limited to, CRFs, source documents, informed consent forms, drug accountability records, IRB correspondence, etc.) for at least 2 years after all investigations have been discontinued. Study records must be stored in a safe and secure location permitting timely retrieval, if necessary.

Study records that must be retained include case report forms, signed informed consents, correspondence with the IRB, study drug dispensing and inventory records, source documents (clinic charts, medical records, laboratory results, radiographic reports) and screening/ enrollment logs.

15.6 Study Termination

The investigator reserves the right to terminate the study at any site and at any time. Reasons for study termination may include, but are not limited to, the following:

- Investigator non-compliance with the protocol, GCP or regulatory requirements
- Insufficient enrollment
- Safety concerns

- Decision by Janssen Research & Development to modify or discontinue the development or manufacturing of erdafitinib
- A request to discontinue the study by the IRB or FDA

The investigator will promptly notify Pfizer, Janssen Research & Development, the IRB and FDA if the study is terminated for any reason.

15.7 Ethics and GCP

This study will be carried out in compliance with the protocol and Good Clinical Practice, as described in:

- ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996
- US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations)
- Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996)

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice to which it conforms.

15.8 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

16. MULTI-CENTER GUIDELINES

16.1 Study Documentation

Each participating site is responsible for submitting copies of all relevant regulatory documentation to the Coordinating Center. The required documents include, but are not limited to the following: local IRB approvals (i.e., protocol, consent form, amendments, patient brochures and recruitment material, etc.), each participant's informed consent, enrollment form, eligibility checklist and tissue block registration, summary of unanticipated problems or protocol deviations, and documentation of expertise of the investigators. The Coordinating Center will provide each participating site with a comprehensive list of the necessary documents. It is the responsibility of the participating sites to maintain copies of all documentation submitted to the Coordinating Center.

The requirements for data management, submissions, and monitoring are outlined below. The TBCRC participating sites will submit all the research related information (source documents and research records – IRB approval documents, patient registration list, CRF info, toxicity assessments, tumor measurements/ responses, etc.) within 2 weeks of the patient's visit to the Coordinating Center Data Manager, who will upload it on Oncore at the appropriate time points: prior to study initiation, when patients are enrolled, and monthly throughout the study. The Coordinating Center Data Manager will have data entered into Oncore within 1 week of receiving the information. Personnel from the VICC Clinical Trial Shared Resource will monitor the trial and may periodically visit the investigative site to assure proper conduct of the trial and proper

collection of the data. The investigators at other sites will allow the monitor to review all source documents used in the preparation of the case reports.

16.2 Records Retention

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by each Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the study is discontinued and the U.S. FDA and the applicable national and local health authorities are notified.

Following closure of the study, each participating center will maintain a copy of all site study records in a safe and secure location. The Coordinating Center will inform the investigator at each site at such time that the records may be destroyed.

16.3 Publication

It is understood that any manuscript or releases resulting from the collaborative research will be circulated to all participating sites prior to submission for publication or presentation.
Any formal presentation or publication of data from this trial may be published after review and comment by Janssen Research & Development and prior to any outside submission. Janssen Research & Development will receive copies of any intended communication in advance of publication (at least twenty-one working days for presentational materials and abstracts and thirty working days for manuscripts). Principal Investigator/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of Janssen Research & Development and, in accord with the trial contract shall not permit disclosure of Pfizer, Inc. and Janssen Research & Development confidential or proprietary information. Additionally, any publication of study data and results must conform to the publications policy as stated the Translational Breast Cancer Research Consortium's (TBCRC) "Policies and Procedures".

17. STATISTICAL CONSIDERATIONS

17.1 Study Design/ Endpoints

This is an open-label phase Ib multi-institution trial that evaluates the safety profile/tolerability (DLT, MTD and RP2D determination) and anti-tumor effect (PFS, CBR and ORR determination) of the combination of palbociclib, fulvestrant and erdafitinib in post-menopausal patients with ER+/HER2-/*FGRF*-amplified metastatic breast cancer. Since a phase II study is currently being planned, tolerability and experience with this combination over a period of time of at least 8-16 weeks is desirable. Hence, in addition to an MTD, we are proposing a "highest tolerable dose", to minimize the risk for unexpected DLT and ensure good tolerability of study drugs in future phase II trials.

17.2 Sample Size and Statistical Analysis

17.2.1 Primary endpoint

Demographic and baseline patient characteristics will be summarized. Adverse events will be classified by type, incidence, severity, and causality. All adverse events will be summarized by patient, dose level, and disease. All patients who received at least 4 weeks of study treatment drugs (unless DLTs observed) will be included in the **safety** portion of the trial, and all patients who received at least 8 weeks of erdafitinib will be included in the **tolerability** portion of the trial.

In the phase Ib escalation component of the trial, the MTD will be defined using the recently developed adaptive design known as the modified toxicity probability interval (mTPI) method[48]. The mTPI design uses a Bayesian framework with a beta/binomial hierarchical model to compute the posterior probabilities of three intervals that reflect the relative distance between the toxicity rate of each dose level to the target toxicity probability. That is, the mTPI design replaces the 3 + 3 rules with a model-based inference on the toxicity probability intervals and has been shown to be safer and more reliable than the 3+3 design. The first cohort of patients (3 patients) in each arm will be started at dose level 1, and each patient will be observed for 4 weeks on the specified dose. The maximum tolerated dose (MTD) will be defined as the highest dose at which 20% of the patients experienced a DLT. The levels of uncertainty around the true target toxicity p_T are (0.05, 0.05), which deifine the proper dosing interval as $(p_T - 0.05, p_T + 0.05)$. Each cohort has 3 patients. In **Table 17.2.1**, the columns are the numbers of patients treated so far at the current dose level, and the rows are the corresponding numbers of patients experiencing toxicity. The entries of the table are dose-finding decisions—E, S, and D—representing escalating the dose, staying at the same dose, and de-escalating the dose, respecitvely. In addition, decision U means that the current dose level is unacceptable because of high toxicity and should be excluded from the trial. For example, when one of three patients experiences toxicity, the decision is to stay at the current dose level. This means that the next cohort of 3 patients will be treated at the same dose level currently being used. If zero of three patients experiences toxicity, the decision is to escalate. This means that the next cohort of 3 patients will be treated at the next-higher dose level. If three of three patients experiences toxicity, the decision is DU—to de-escalate to the next-lower dose level and exclude the current dose from the trial which is considered unacceptably toxic.

Table 17.2.1

Number of Patients																		
Number of Patients with DLTs	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	D	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E
2		D	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	E	E
3			DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S
4				DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S
5					DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S	S	S
6						DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S
7							DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
8								DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
9									DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
10										DU	DU	DU	DU	DU	DU	DU	DU	DU
11											DU	DU	DU	DU	DU	DU	DU	DU
12												DU	DU	DU	DU	DU	DU	DU
13													DU	DU	DU	DU	DU	DU
14														DU	DU	DU	DU	DU
15															DU	DU	DU	DU

16															DU	DU	DU
17																DU	DU
18																	DU

E: Escalate to the next higher dose; S: Stay at the same dose; D: De-escalate to the previous lower dose; DU: De-escalate to the previous lower dose and the current dose will never be used again in the trial;

No new cohort of patients will be treated until the previous cohort has been fully evaluated for toxicity. All patients treated to determine the MTD will be part of the escalation portion of the trial.

Once the MTD is reached, the safety data will be analyzed and the expansion component of the study will be completed to assess tolerability and efficacy. Patients in the expansion component of the study will initiate study treatment at the respective MTD. Note that dose reduction within individual patients is allowed in the expansion component of the study. Dose reduction will be required for a given patient in case of grade 3 or 4 toxicities, or if grade 2 creatinine, bilirubin, AST, ALT, hyperphosphatemia or grade 2 GI toxicity lasting more than 2 weeks.

Since a phase II study is currently being planned, tolerability and experience with these combinations over at least 8-16 weeks is desirable. A period of 8 weeks was deemed acceptable for assessment of study drug tolerability. Hence, we are proposing a modified definition of an MTD, to ensure tolerability of study drugs for a more prolonged period of time in anticipation of future phase II trials. We plan to treat at least 20 patients as part of the expansion portion of the study. For tolerability assessment, patients in the escalation portion of the trial that are treated at the MTD will be included in the tolerability analysis.

Justification for RP2D based on ≥ 15 out of 20 Tolerant Patients

		True probability of tolerability at MTD					
	0.3	**0.5**	**0.7**	**0.75**	**0.8**	**0.9**	**0.99**
Probability of observing ≥ 15/20 tolerable patients	0.00004	0.02	0.42	0.62	0.80	0.99	1.00

Two-sided 95% Wilson Confidence Intervals* for the Probability of Treatment Tolerance based on ≥15 Tolerant Patients out of 20

Observed # of tolerant patients	95% Wilson confidence interval	
	Lower bound	Upper bound
15	0.53	0.89
16	0.58	0.92
17	0.64	0.95
18	0.70	0.97
19	0.76	0.99
20	0.84	1.00

* We chose to calculate and report the Wilson score confidence intervals[49] because of their good coverage properties, especially when the true proportions are at extreme values such as

being equal to or close to 1
[50](http://en.wikipedia.org/wiki/Binomial_proportion_confidence_interval).

The recommended dose for phase II trials will be defined as the highest dose (at or below the MTD) at which ≥ 15 patients treated at the MTD (including patients from the escalation portion treated at that same dose level) can tolerate treatment for a minimum of 8 weeks in a row without development of the previously cited toxicities. The dose that will be used in the phase II study will be the most tolerable (i.e. with the least amount of ≥ Grade 2 toxicities), as tested in this study. Study drugs will be given at the specified doses above until disease progression or unacceptable toxicity. As long as the above parameters are fulfilled (i.e. at least 15 out 20 patients are able to safely tolerate the combination at a given dose level stipulated by the study for 8 weeks in a row) the dose of study drugs in the expansion portion of the study (i.e. the highest tolerable dose; not necessarily the MTD) will move forward in phase II studies.

17.2.2. Secondary endpoints

Secondary endpoints defined in terms of percentages such as Overall Response Rate (ORR), Clinical Benefit Rate (CBR), and Progression-Free Survival (PFS) will be summarized and 95% CI for each percentage will be reported. The distribution of PFS will be estimated using the Kaplan-Meier method with censoring used as needed (e.g. if a patient is lost to follow-up, or analysis is done before all patients have had the event of interest). Median time to event and corresponding 95% CI will be reported along with Kaplan-Meier curves. The duration of PFS for patients who progress and then subsequently die will be the number of days between initiation of the study treatment and the date of when disease progression is first observed. Demographic and clinical characteristics will be summarized for all patients as percentages for categorical variables and as mean, standard deviation, median, minimum and maximum for continuous measures. Data will be collected using a centralized electronic case report form called **ON**-line **C**linical **O**ncology **R**esearch Environment = **Oncore** (http://www.vicc.org/ct/research/oncore.php). An exploratory objective of this study is to determine the pharmacokinetics of the combination of erdafitinib, palbociclib and fulvestrant. The plasma samples from all patients will be assayed for erdafitinib and palbociclib concentrations using methods described in the Laboratory manual. Values below the assay LLOQ will be reported as 0.00 ng/mL. Missing values will be labeled accordingly. All concentrations below the LLOQ or missing data will be labeled as such in the concentration data listings. Concentrations below the LLOQ will be treated as zero in summary statistics. Calculation of PK parameters will include up to the last measurable concentration t_{last}. Pharmacokinetic parameters will be determined for all patients using non-compartmental method(s) using WinNonlin® Pro (Version 5.2 - Pharsight, Mountain View, CA). PK parameters listed in the table below will be estimated and reported.

$AUC_{0\text{-}last}$	The area under the plasma concentration-time curve from time zero to the last measurable concentration (T_{last}) (mass x time x volume $^{-1}$)
$AUC_{0\text{-}Inf}$	The area under the plasma concentration-time curve from time zero to infinity (mass x time x volume $^{-1}$)
$AUC_{0\text{-}24}$	The area under the plasma concentration-time curve from time zero to 24 hours (mass x time x volume $^{-1}$)
AUC_{ex}[1]	Area under the plasma concentration-time curve extrapolated from the time t to infinity as a percentage of total AUC (%)
C_{av}	The average drug concentration in plasma during the dosing interval (mass x volume $^{-1}$)
C_{last}	Last measurable plasma concentration

C_{max}	The maximum (peak) observed plasma drug concentration after oral dose administration (mass x volume $^{-1}$)
T_{last}	Time to reach the last measurable plasma concentration
T_{max}	The time to reach maximum (C_{max}) plasma drug concentration after oral dose administration (time)
CL/F	Apparent total body clearance of drug from the plasma after oral administration (volume x time $^{-1}$)
Vz/F	The apparent volume of distribution during terminal phase after a (single) oral administration (associated with λz) (volume)
Rsqadj[1]	Square of the correlation coefficient associated with λz
[1] AUC_{ex} and Rsqadj will be used in interpretation of the primary PK parameters and therefore will be included in the listings only	

Exploratory PK analysis will be conducted using compartmental modeling when necessary. Descriptive graphical plots of individual and mean plasma concentration (per treatment) along with its time course will be generated. Further graphical exploratory analyses will be carried out if deemed appropriate. Pharmacokinetic parameters for each dose cohort will be analyzed by descriptive statistics, including the mean, SD, CV% or median (range). Since t_{max} is generally evaluated by a non-parametric method, median values and ranges will be given for this parameter. Assessment of dose-proportionality, inter- and intra-individual variability and steady-state attainment will be conducted. If appropriate, an analysis of variance (ANOVA) will be performed on log-transformed AUCs and C_{max} using a linear mixed effect model to assess day effect. Exploratory metabolite analysis on remaining plasma material from samples collected during the study will be performed, if deemed appropriate. Non-compartmental parameters, including but not limited to AUC (AUC0-tlast and/or AUC0-inf), T1/2, C_{max} and T_{max} will be reported.

17.3 Reporting and Exclusions

All patients included in the study must be assessed for safety, tolerability, and response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response and clinical benefit rate.

18. REFERENCES

1. American Cancer Society Cancer Facts and Figures *Atlanta, GA: American Cancer Society, 2011.*
2. Sorlie, T.*, et al.* Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci U S A* **98**, 10869-10874 (2001).
3. Howell, A. & Abram, P. Clinical development of fulvestrant ("Faslodex"). *Cancer treatment reviews* **31 Suppl 2**, S3-9 (2005).
4. Dowsett, M., Nicholson, R.I. & Pietras, R.J. Biological characteristics of the pure antiestrogen fulvestrant: overcoming endocrine resistance. *Breast Cancer Res Treat* **93 Suppl 1**, S11-18 (2005).
5. Miller, T.W.*, et al.* ERalpha-dependent E2F transcription can mediate resistance to estrogen deprivation in human breast cancer. *Cancer discovery* **1**, 338-351 (2011).
6. Huang, B., Warner, M. & Gustafsson, J.A. Estrogen receptors in breast carcinogenesis and endocrine therapy. *Mol Cell Endocrinol* **418 Pt 3**, 240-244 (2015).
7. Ishida, N.*, et al.* Fulvestrant 500 mg in postmenopausal patients with metastatic breast cancer: the initial clinical experience. *Breast Cancer* (2015).
8. Agrawal, A.*, et al.* Biological effects of fulvestrant on estrogen receptor positive human breast cancer: short, medium and long-term effects based on sequential biopsies. *Int J Cancer* **138**, 146-159 (2016).
9. Tan, P.S., Haaland, B., Montero, A.J. & Lopes, G. A meta-analysis of anastrozole in combination with fulvestrant in the first line treatment of hormone receptor positive advanced breast cancer. *Breast Cancer Res Treat* **138**, 961-965 (2013).
10. Di Leo, A.*, et al.* Final overall survival: fulvestrant 500 mg vs 250 mg in the randomized CONFIRM trial. *J Natl Cancer Inst* **106**, djt337 (2014).
11. Yardley, D.A.*, et al.* Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. *Advances in therapy* **30**, 870-884 (2013).
12. Turner, N.C.*, et al.* Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. *N Engl J Med* **373**, 209-219 (2015).
13. Fry, D.W.*, et al.* Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. *Mol Cancer Ther* **3**, 1427-1438 (2004).
14. Schwartz, G.K.*, et al.* Phase I study of PD 0332991, a cyclin-dependent kinase inhibitor, administered in 3-week cycles (Schedule 2/1). *Br J Cancer* **104**, 1862-1868 (2011).
15. Dean, J.L., Thangavel, C., McClendon, A.K., Reed, C.A. & Knudsen, E.S. Therapeutic CDK4/6 inhibition in breast cancer: key mechanisms of response and failure. *Oncogene* **29**, 4018-4032 (2010).
16. Finn, R.S.*, et al.* PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. *Breast Cancer Res* **11**, R77 (2009).
17. Finn, R.S.*, et al.* The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol* **16**, 25-35 (2015).
18. Wardell, S.E.*, et al.* Efficacy of SERD/SERM Hybrid-CDK4/6 Inhibitor Combinations in Models of Endocrine Therapy-Resistant Breast Cancer. *Clin Cancer Res* **21**, 5121-5130 (2015).
19. Flaherty, K.T.*, et al.* Phase I, dose-escalation trial of the oral cyclin-dependent kinase 4/6 inhibitor PD 0332991, administered using a 21-day schedule in patients with advanced cancer. *Clin Cancer Res* **18**, 568-576 (2012).

20. DeMichele, A.*, et al.* CDK 4/6 inhibitor palbociclib (PD0332991) in Rb+ advanced breast cancer: phase II activity, safety, and predictive biomarker assessment. *Clin Cancer Res* **21**, 995-1001 (2015).
21. Finn, R.S.*, et al.* PALOMA-2: Primary results from a phase III trial of palbociclib (P) with letrozole (L) compared with letrozole alone in postmenopausal women with ER+/HER2– advanced breast cancer (ABC). *J Clin Oncol* **34 (suppl; abstract 507)**(2016).
22. Turner, N.C., Huang Bartlett, C. & Cristofanilli, M. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. *N Engl J Med* **373**, 1672-1673 (2015).
23. Cristofanilli, M.*, et al.* Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol* (2016).
24. Chia, S.*, et al.* Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. *J Clin Oncol* **26**, 1664-1670 (2008).
25. Beenken, A. & Mohammadi, M. The FGF family: biology, pathophysiology and therapy. *Nat Rev Drug Discov* **8**, 235-253 (2009).
26. Turner, N. & Grose, R. Fibroblast growth factor signalling: from development to cancer. *Nat Rev Cancer* **10**, 116-129 (2010).
27. Comprehensive molecular portraits of human breast tumours. *Nature* **490**, 61-70 (2012).
28. Turner, N.*, et al.* FGFR1 amplification drives endocrine therapy resistance and is a therapeutic target in breast cancer. *Cancer Res* **70**, 2085-2094 (2010).
29. Kwek, S.S.*, et al.* Co-amplified genes at 8p12 and 11q13 in breast tumors cooperate with two major pathways in oncogenesis. *Oncogene* **28**, 1892-1903 (2009).
30. Cuny, M.*, et al.* Relating genotype and phenotype in breast cancer: an analysis of the prognostic significance of amplification at eight different genes or loci and of p53 mutations. *Cancer Res* **60**, 1077-1083 (2000).
31. Tabernero, J.*, et al.* Phase I Dose-Escalation Study of JNJ-42756493, an Oral Pan-Fibroblast Growth Factor Receptor Inhibitor, in Patients With Advanced Solid Tumors. *J Clin Oncol* **33**, 3401-3408 (2015).
32. Johannessen, C.M.*, et al.* COT drives resistance to RAF inhibition through MAP kinase pathway reactivation. *Nature* **468**, 968-972 (2010).
33. Andre, F.*, et al.* Targeting FGFR with dovitinib (TKI258): preclinical and clinical data in breast cancer. *Clin Cancer Res* **19**, 3693-3702 (2013).
34. Soria, J.C.*, et al.* Phase I/IIa study evaluating the safety, efficacy, pharmacokinetics, and pharmacodynamics of lucitanib in advanced solid tumors. *Ann Oncol* **25**, 2244-2251 (2014).
35. Andre, F.*, et al.* A multicenter, open-label phase II trial of dovitinib, an FGFR1 inhibitor, in FGFR1 amplified and non-amplifi ed metastatic breast cancer. *J Clin Oncol* **29**(2011).
36. Schwarzenbach, H., Hoon, D.S. & Pantel, K. Cell-free nucleic acids as biomarkers in cancer patients. *Nat Rev Cancer* **11**, 426-437 (2011).
37. Gormally, E., Caboux, E., Vineis, P. & Hainaut, P. Circulating free DNA in plasma or serum as biomarker of carcinogenesis: practical aspects and biological significance. *Mutat Res* **635**, 105-117 (2007).
38. Dawson, S.J.*, et al.* Analysis of circulating tumor DNA to monitor metastatic breast cancer. *N Engl J Med* **368**, 1199-1209 (2013).
39. Dienstmann, R.*, et al.* Genomic aberrations in the FGFR pathway: opportunities for targeted therapies in solid tumors. *Ann Oncol* **25**, 552-563 (2014).

40. Schildhaus, H.U.*, et al.* Definition of a fluorescence in-situ hybridization score identifies high- and low-level FGFR1 amplification types in squamous cell lung cancer. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc* **25**, 1473-1480 (2012).
41. Katoh, M. WNT and FGF gene clusters (review). *Int J Oncol* **21**, 1269-1273 (2002).
42. Brady, N., Chuntova, P., Bade, L.K. & Schwertfeger, K.L. The FGF/FGFR axis as a therapeutic target in breast cancer. *Expert Rev Endocrinol Metab* **8**, 391-402 (2013).
43. Herrera-Abreu, M.T.*, et al.* Early Adaptation and Acquired Resistance to CDK4/6 Inhibition in Estrogen Receptor-Positive Breast Cancer. *Cancer Res* **76**, 2301-2313 (2016).
44. Robinson, D.R.*, et al.* Activating ESR1 mutations in hormone-resistant metastatic breast cancer. *Nat Genet* **45**, 1446-1451 (2013).
45. Jeselsohn, R.*, et al.* Emergence of constitutively active estrogen receptor-alpha mutations in pretreated advanced estrogen receptor-positive breast cancer. *Clin Cancer Res* **20**, 1757-1767 (2014).
46. Cheng, D.T.*, et al.* Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT): A Hybridization Capture-Based Next-Generation Sequencing Clinical Assay for Solid Tumor Molecular Oncology. *J Mol Diagn* **17**, 251-264 (2015).
47. Eisenhauer, E.A.*, et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* **45**, 228-247 (2009).
48. Ji, Y. & Wang, S.J. Modified toxicity probability interval design: a safer and more reliable method than the 3 + 3 design for practical phase I trials. *J Clin Oncol* **31**, 1785-1791 (2013).
49. Wilson, E.B. Probable inference, the law of succession, and statistical inference. *Journal of the American Statistical Association* **22**, 209-212 (1927).
50. Newcombe, R.G. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stat Med* **17**, 857-872 (1998).

19. MEDICATIONS TO BE USED WITH CAUTION

Please note this is not an exhaustive list. Alternatives to concurrent administration of erdafitinib and the below medications should be sought; if no alternative treatment is available, the Study Chair should be consulted.

Moderate and Strong CYP3A4 Inhibitors:

Aprepitant
Atazanavir
Boceprevir
Clarithromycin
Cobicastat
Conivaptan
Diltiazem
Erythromycin
Fluconazole
Fosamprenavir
Grapefruit Juice
Idelalisib
Imatinib
Indinavir
Itraconazole
Ketoconazole
Lopinavir
Nefazodone
Nelfinavir
Nilotinib
Posaconazole
Ritonavir
Saquinavir
Suboxone
Telaprevir
Telithromycin
Verapamil
Voriconazole

Moderate and Strong CYP3A4 Inducers:

Bosentan
Carbamazepine
Efavirenz
Enzalutamide
Fosphenytoin
Lumacaftor
Mitotane
Modafanil
Nafcillin
Phenytoin
Phenobarbital
Primidone
Rifampin
Rifapentin
St. John's Wort

Moderate and Strong CYP2C9 Inhibitors:

Amiodarone
Delaviridine
Efavirenz
Fluconazole
Fluvastatin
Miconazole

Moderate and Strong CYP2C9 Inducers:

Enzalutamide
Phenobarbital
Primidone
Rifapentin

Moderate and Strong P-gp Inhibitors:

Amiodarone
Clarithromycin
Erythromycin

Moderate and Strong P-gp Inducers:

Carbamazepine
Rifampin
St. John's wort

Ketoconazole
Quinidine
Saquinavir
Verapamil
Tipranavir