Request for Proposal

A Multi-Center, Randomized, Open-Label, Phase 2b Study of Elacestrant versus Standard of Care in Patients with Estrogen Receptor Positive, HER2 Negative Metastatic Breast Cancer

Data and Clinical Coordinating Center
University of Washington
Seattle, WA 98195

[6/1/22]

Table of Contents

Protocol Team Roster

Katie McFarlane

Co-Lead Biostatistician

knmcfar@uw.edu

Jiayu Sun

Co-Lead Biostatistician

jiayusun@uw.edu

Iyabode Tiamiyu

Principal Investigator

iyabode@uw.edu

Jessica Ziemek

Site Visit Chair

jziemek@uw.edu

List of Abbreviations and Acronyms

AE	Adverse Event
AI/AN	American Indian or Alaska Native
CAP	Chest Abdomen and Pelvis
CBC	Complete Blood Count
CBE	Clinical Benefit-Evaluable
CBR	Clinical Benefit Rate
CDK4/6	Cyclin Dependent Kinase 4/6
CIP	Cancer Imaging Program
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP-AERS	Cancer Therapy Evaluation Program Adverse Event Reporting System
DCP	Division of Cancer Prevention
DCTD	Division of Cancer Treatment and Diagnosis
DMC	Data Monitoring Committee
DoR	Duration of Response
EC	Ethics Committee
EORTC	European Organisation for the Treatment of Cancer
ER	Estrogen Receptor
ESR1	Estrogen Receptor 1
FAERS	Food and Drug Administration Adverse Event Reporting System
FDA	Food and Drug Administration
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hormone Receptor
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IHC	Immunohistochemistry
IM	Intramuscularly
IND	Investigational New Drug
IRB	Institutional Review Board
IWRS	Interactive Web Response System
JAMA	Journal of the American Medical Association

LFT	Liver Function Test
MRI	Magnetic Resonance Imaging
MNAR	Missing Not At Random
NCI	National Cancer Institute
NHPI	Native Hawaiian or Pacific Islander
OS	Objective Survival
PD	Progressive Disease
PFS	Progression Free Survival
PI	Principal Investigator
PK	Pharmacokinetics
PR	Progesterone Receptor
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
SERD	Selective Estrogen Receptor Degrader
VTE	Venous Thromboembolic Events
WC	Withdrawal of Consent

Synopsis

Purpose: To evaluate the efficacy and safety of elacestrant as compared to standard of care as assessed by progression-free survival

Design: A randomized, open-label, phase 2b study

Study Population: Postmenopausal adult patients with ER+/HER2- advanced breast cancer who are CDK4/6 inhibitor naive

Study Size: 300 patients will be enrolled in a 1:1 ratio of elacestrant as compared to standard of care

Treatment Regimen: Daily oral administration of elacestrant (400 mg) or clinician's choice of standard of care

Study Duration: 2 years

Primary Objectives:

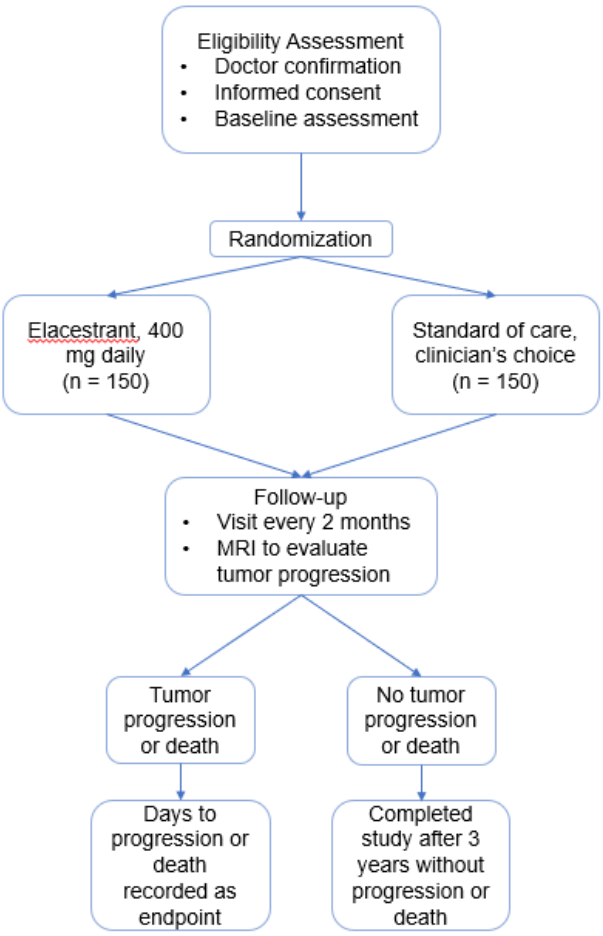
- Progression Free Survival (PFS)

Secondary Objectives:

- Overall survival (OS)
- Duration of response (DoR)
- Safety and tolerability
- Quality of life measures as reported by use of a smartwatch
- Pharmacokinetics of elacestrant and its metabolites

Study Sites: 30 total sites located internationally

Study Schema



1. Background

1a. Study Disease

Breast cancer is the most common cancer type in the world. It accounts for about 30% of female cancers with a mortality-to-incidence ratio of 15%. In the United States, breast cancer will be diagnosed in 12% of women over the course of their lifetimes. Breast cancer is very heterogeneous and can be clinically categorized into three major subtypes based on the presence or absence of molecular markers for estrogen or progesterone receptors (ER or PR) and human epidermal growth factor 2 (HER2): hormone receptor (HR) positive/HER2 negative (70% of patients), HER2 positive (15%-20% of patients), and triple-negative (tumors lacking all 3 standard molecular markers; 15% of patients). More than 90% of breast cancers are not metastatic at the time of diagnosis, and about 6% of breast cancers are metastatic at the time of diagnosis, defined as involvement of sites distant from the breast and its regional lymph nodes. Metastatic breast cancers have median overall survival of approximately 5 years for HR+ or HER2+ subtypes and 1 year for triple-negative subtype. More than 150, 000 women in the United States are living with a diagnosis of metastatic breast cancer, and nearly 41, 000 deaths from breast cancer occur annually, virtually all due to metastatic disease (Loibl et al., Waks et al.).

For people presenting without metastatic disease, therapeutic goals are tumor eradication and preventing recurrence, while metastatic breast cancer is treated with goals of prolonging life and palliating symptoms. The standard regimens used in the treatment of metastatic breast cancer vary by subtypes. A CDK4/6 inhibitor combined with endocrine therapy is considered a standard of care for patients with ER positive, HER2 negative metastatic breast cancer. Anti-HER2 therapy, in combination with either chemotherapy or endocrine therapy, is recommended for treating HER2-positive metastatic breast cancer. For triple-negative metastatic breast cancer, chemotherapy is usually the standard of care (Loibl et al., Waks et al.).

Despite the remarkable advancements made in developing treatment options for patients with metastatic breast cancer, associated toxicities remain a treatment-limiting factor. As demonstrated in a meta-analysis of CDK4/6 inhibitor use in approximately 5,000 randomized, clinical trial patients, this preferred first-line therapeutic class carries an increased risk of neutropenia, leukopenia, and/or diarrhea (Li et al.). Long-term pooled safety data from the

PALOMA randomized phase 2 and 3 studies show that 8.3% of patients required permanent discontinuation due to adverse events (AEs). In addition, 37% of patients required AE associated dose reductions of palbociclib when administered in conjunction with endocrine therapy (Diéras et al.). A similar trend in discontinuation rates has been reported for the ribociclib MONALEESA studies and abemaciclib MONARCH trials (Tripathy et al., Goetz et al.). In the MONARCH 2 and MONARCH 3 phase 3 trials investigating abemaciclib in combination with endocrine therapy, this discontinuation rate notably increases with advanced age, with 14.2% of patients between 65-74 years of age and 24.1% of patients 75 and above discontinuing study treatment due to a treatment-limiting AE (Goetz et al.). More recently, emerging real-world evidence suggests an increased risk in venous thromboembolic events (VTEs) for patients treated with CDK4/6 inhibitors. In a retrospective analysis of the Food and Drug Administration adverse event reporting system (FAERS) and multicenter retrospective analysis, this VTE risk has steadily increased with time, as CDK4/6 inhibitors have been increasingly adopted in use (Raschi et al.). Importantly, in the multicenter retrospective analysis of thrombosis with CDK4/6 inhibition use, an incidence rate of 10.9%, 8.3%, and 4.8% was reported for palbociclib, ribociclib, and abemaciclib, respectively (West et al.).

In totality, the discontinuation rates in randomized clinical trials of patients with arguably better controlled disease activity and fewer comorbidities than the general metastatic breast cancer population alongside emerging safety findings underscore the importance of additional efficacious, well-tolerated, and convenient treatment options.

1b. Rationale for Use of Elacestrant

Elacestrant is a nonsteroidal, oral selective estrogen receptor degrader (SERD) with pre-clinical antitumor activity and clinical activity in early phase evaluation. In estrogen receptor (ER) positive breast cancer cell lines, elacestrant induces ER degradation, thereby inhibiting ER-mediated signaling and downstream proliferative activity (Bihani et al.). In a multicenter, open-label, phase 1 dose-escalation study in female patients with ER+, human epidermal growth factor receptor 2 negative metastatic breast cancer, elacestrant was well tolerated and exhibited antitumor activity when administered at 400 mg daily. Among the 50 patients that received this dose, 47 were clinical benefit-evaluable (CBE), of which a clinical benefit rate (CBR) was observed in approximately 43 percent of patients. In CDK4/6i naïve patients, the CBR was 54.2% as compared to CDK4/6i, which conferred a CBR of 30.4%. Furthermore, in the intent-to-treat patient population, median progression-free survival (PFS) in CDK4/6i naïve patients was 7.4 months, versus 3.8 months in CDK4/6i experienced patients (Bardia et al.).

1c. Rationale for Use of Standard of Care as Comparator

This study will use standard of care in comparison to elacestrant, as current approved treatments do exist for this study population, and it would be unethical to deny participants current standard of care. A placebo is not used in this study design, as it would be burdensome for participants to undergo standard of care in addition to either elacestrant or placebo.

1d. Study Question

The study is intended to answer the following scientific question: In adult female patients with ER+/HER2- advanced breast cancer, how does either daily oral administration of 400 mg of elacestrant as compared to standard of care affect patients' progression-free survival (PFS) within up to a two-year time period?

2. Objectives

2a. Primary Objective

The primary objective of this study is to assess the efficacy of elacestrant as compared to standard of care estrogen receptor targeted therapy, with respect to PFS.

2b. Secondary Objectives

The secondary objectives of the study are to compare both treatment groups, with respect to each of the following:

- Overall survival (OS)
- Duration of response (DoR)
- Safety and tolerability
- Patient-reported quality of life measures
    - Euro-Qol-5 Dimension-5 Level (EQ-5D-5L) (see Appendix C for a sample)
    - European Organisation for the Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30)
- Quality of life measures as reported by use of a smartwatch
    - Sleep data and physical activity data
- Pharmacokinetics (PK) of elacestrant and its metabolites

2c. Exploratory Objectives

Exploratory objectives include:

- Evaluation of potential biomarkers associated with tumor response, including baseline estrogen receptor 1 (ESR1) mutation status

3. Study Design

3a. Overall Design

This is a Phase 2b, randomized, open-label multicenter study to assess the efficacy and safety of elacestrant as compared to standard of care estrogen receptor targeted therapy in adult female patients with ER+/HER2- advanced breast cancer. Approximately 300 patients who meet the following entry criteria will be enrolled at 30 research sites across the globe.

3b. Eligibility Criteria

Inclusion Criteria

Patients are eligible for inclusion in this study only if they meet all of the criteria that follow:

1. Provide written informed consent before any study-specific procedures
2. Female sex, ≥ 18 years of age, and postmenopausal
    a. Postmenopausal status must be due to either surgical/natural menopause or as a result of ovarian suppression that has been initiated for 28 days or more than day 1 of the study
3. HR+, HER2- breast cancer
    a. HR+ disease must either be documented in the patient's medical history as ER+ (≥ 1% staining by immunohistochemistry (IHC)) or for patients that present with de novo, previously untreated, metastatic disease, confirmed prior to randomization
    b. HER2- disease must either be documented in the patient's medical history or for patients that present with de novo, previously untreated, metastatic disease, confirmed prior to randomization
4. Metastatic breast adenocarcinoma with measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1)
5. Eastern Cooperative Group performance status of 0-2
6. Discontinuation of prior anti-cancer therapies according to the windows below
    a. Endocrine therapy for 14 days or more prior to day 1
    b. Chemotherapy for 28 days or more prior to day 1
7. Discontinuation of strong cytochrome 3A4 inducers or inhibitors for 7 days or more prior to day 1
8. Able to swallow tablets

Exclusion Criteria

Patients must be excluded from this study if they meet any of the criteria that follow:

1. Are currently receiving an investigational drug or have received an investigational drug within 28 days prior to day 1
2. Historical use of a CDK4/6 inhibitor at any time
3. Grade 3 or greater lab abnormalities, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0
4. Untreated or symptomatic central nervous system metastases
5. Endometrial disorders, including but not limited to endometrial hyperplasia, dysfunctional uterine bleeding, or cysts
6. Any serious preexisting medical condition or procedure that, according to the investigator should preclude participation (including factors associated with patient safety, adherence/compliance)
7. Are pregnant or breastfeeding

Those who fit this eligibility criteria will be randomly allocated in a ratio of 1:1 to receive open-label treatment of elacestrant or standard of care. There will be a 28-day screening window for enrolling patients, after which patients should begin taking regular dosages of elacestrant or standard of care treatment as determined by a clinician. Patients randomized to receive elacestrant will receive 400 mg orally, while patients receiving standard of care will receive comparable care, with dosages according to clinicians' decisions (see Treatment section 3g for more information).

3c. Co-Enrollment Guidelines

Participants should not be enrolled in other investigation drug trials throughout the course of their enrollment in this clinical trial. This is due to multiple reasons:

- The effects of other experimental treatments may interfere with the effects of elacestrant or standard of care on patients in ways that are unpredictable (Myles et al.)
    - Data on the safety profile of elacestrant is still being collected in this trial, and taking elacestrant concurrently with other experimental drugs could cause patients to experience AEs
- Taking more than one experimental treatment compromises the ability of the trial to determine the efficacy of elacestrant as compared to standard of care through the statistical methods explained in section 4: Statistical Analysis Plan

- Enrollment in multiple trials may place an undue burden on participants, leading to lower adherence rates in these trials

Patients can withdraw their consent to participant in this trial at any time if they wish to enroll in a separate investigational drug trial.

3d. Participant Recruitment, Retention, and Withdrawal

Recruitment

Recruitment will take place across 30 sites globally and is anticipated to take 12 months to complete, with an estimate of enrolling approximately 10 patients per site. Recruitment strategies will include medical record review, mass media distribution, a study website, and mailings to referring providers to aid in identification of potential participants. Recruitment strategies and site contact will be managed by a recruitment coordinator.

Medical record review: Study site staff will be expected to review medical records at their sites to screen for eligibility and report monthly screening logs to the recruitment coordinator. Screening logs will include the number of patients pre-screened each month, whether or not the individual pre-screened was eligible, reason for ineligibility, if the potentially eligible individual consented to the study, and reasons for non-consent if the potentially eligible participant did not consent.

Mass Media Distribution: Ads for the study will be created for distribution on social media, radio, and television in the referral areas of research sites. Visual ads will include a link/QR code to the study informational website. Additionally, study sites will be provided with flyers, pamphlets, and posters to be placed in their clinic for patient review.

Study Website: Mass media distribution will reference the study informational website. This website will include a brief overview of the study, a list of participating research sites, and contact information for participating research sites. The recruitment coordinator will review the number of webpage visits the website receives.

Mailings to referring providers: Study sites will be provided with postcard-sized informational cards that can be mailed to referring providers to notify and educate community partners of the potential study opportunity for their patients.

The recruitment coordinator will closely monitor each research site's recruitment and enrollment. If after 6 months a research site has not shown sufficient pre-screening or recruitment efforts, the research site may be closed and additional research sites may be added to meet recruitment goals.

Retention

After enrollment in the study, the study site that enrolled a patient will make all possible efforts to retain that individual in the study for the entirety of the study or until death, in order to reduce potential bias associated with patients being lost to follow-up. This study aims for 90% retention or higher. Each study site will have its own procedure for maintaining this goal, but possible strategies include (though are not limited to) the following:

- Thorough explanations to all participants as to the events that they can expect to undergo throughout the course of the study (see Appendix A: Study Calendar)
- Thorough explanations to all participants as to the aims of this study and potential benefits and disadvantages to entering the study (see Appendix B: Informed Consent Form)
- Thorough explanations to all participants as to the need for both the treatment and standard of care arms
- Personalized care for participants from knowledgeable and trustworthy public health professionals and community members
- Use of visit reminders, including text message, phone calls, or emails, as well as written reminders at the end of each visit
- Immediate follow-up attempts after missed visits, utilizing more than one method of communication
- Reduce the number of visits in the second years of the study (from every two months to every three months) to reduce burden on participants
- Use of technology (such as smartwatches) to reduce the number of times participants must come in for follow-up visits or fill out surveys
- Travel reimbursements for each follow-up visit to reduce the burden of traveling multiple times per year to study sites

Withdrawal

Participants have a right to voluntarily withdraw their consent to remain in the study at any time, regardless of how long they have been in the study or any amount of effort put into retention strategies. In extreme cases, investigators may withdraw patients from the study due to safety concerns or unwillingness to comply with study protocol. Additionally, patients may be withdrawn if the sponsor terminates the study prior to the planned date of completion after DMC recommendation due to any reason or if regulatory authorities decide to terminate the trial.

Patients may, at times, decide to discontinue treatment. Efforts will be made in all cases to retain these participants in the study and continue to follow-up with these individuals. This would not be considered withdrawal from the study, as these individuals will still be included in analyses and will still be maintained in follow-up as originally planned. However, if patients initiate the withdrawal of consent, they are ethically to be excluded from follow-up attempts. See section 4b: Handling of Missing Data for more information on how this missing data is handled in analyses.

3e. Data Capture

This study will utilize an electronic data capture system. Each research site will maintain the respective source records, according to institutional/local documentation requirements. Pertinent clinical trial related information will then be entered into the data capture system in the format of case report forms (CRFs). CRFs will include pages for the informed consent visit, demographic data, medical history, prior medication use, eligibility criteria, on-study visits, follow-up visits, concomitant medications, and adverse events.

Data captured within the CRFs will be in a de-identified format, with each clinic able to access and edit their respective patient CRFs and full viewing access by the trial oversight team.

Each investigator and delegated data entry personnel will be trained on use of the data capture system and provided support resources prior to consenting their first patient.

3f. Quality Assurance

In order to ensure accurate and high-quality data, the trial oversight team will require investigator and sub-investigator training prior to consenting the first patient at each trial location. This training will review elacestrant dosing information and safety monitoring

considerations. In addition, it will thoroughly explain the objectives of the study, required procedures, and for the respective parties, data capture requirements.

The trial oversight team will also provide investigator site support documents, including eligibility checklists and contact information sheets. Furthermore, a contract research organization (CRO) will be utilized to conduct on-site monitoring visits. These visits will commence with an initial initiation visit, prior to the site's first patient visit. Periodic, on-study visits will also take place to review the accurate transcription of source documentation data to the electronic data capture system.

3g. Treatment

Randomization

Upon completion of screening assessments, eligible patients will be randomized 1:1 to the treatment or control arm using an Interactive Web Response System (IWRS). Randomization will be stratified based on prior use of estrogen-receptor directed therapy (SERD, Y vs N).

Treatment Arms

Investigational Product

Subjects in the treatment arm will receive elacestrant orally as a single 400-mg tablet once daily.

Standard of Care

Subjects in the control arm will receive Investigator's choice of one of the Standard of Care drugs: fulvestrant (500 mg administered intramuscularly (IM) into the buttocks as two 5 mL injections (250 mg/5 ml) on days 1 and 15 of Cycle 1, and on day 1 of each subsequent 28 day cycle), anastrozole (1 mg/day on a continuous dosing schedule), letrozole (2.5 mg/day on a continuous dosing schedule), or exemestane (25 mg/day on a continuous dosing schedule).

Discontinuation

Treatments will be continued until disease progression, intolerability, or death, whichever comes first, except in the case that participants wish to withdraw from the study (see Section 3d: Participant Withdrawal).

Treatment Supply and Accountability

Each site pharmacist will maintain records of treatments received from the drug manufacturer as well as all pertinent manufacturing information. These drugs will thus be dispensed to participants per their randomized treatment arm. Unused medication will ultimately be returned to the study site by participants at each follow-up visit and after the study is completed or terminated for adherence assessment and for proper disposal.

Adherence Assessment

Adherence to this study design is described as taking treatments on a regular schedule, attending follow-up visits with a clinician, and working with study employees to complete assessments, to record concomitant medications and side effects/AEs, and to undergo scans and lab work when needed. However, it is known that not all patients are able to adhere to all of these guidelines. Adherence will be assessed in multiple ways, adapted from suggestions from the European Patients' Academy on Therapeutic Innovation ("Assessing Participant Adherence..."):

- Attendance of follow-up visits, or prompt rescheduling of visits when they are missed for any reason
- Review of patient files between visits to ensure appointments have not been missed and all pertinent information was shared by patients
- Returning pill bottles and counting of tablets to assess how strictly the patient has followed the treatment schedule

Toxicity Management

Treatment regimens may need to be adjusted throughout the course of this study due to AEs or side effects due to toxicity of drugs. While the overall aim of the study is to assess the efficacy and safety of daily administration of 400 mg of elacestrant, patient safety and retention is a primary concern. As such, the first step when drug toxicity becomes a problem for patients is to lower the dosage. Patients will work directly with clinicians to determine a dosage that is allowable. Additional options include taking a short break from the treatment regimen (that is, drop out for a short period of time and then drop back in) to allow the patient a chance to recover from side effects. Any changes to treatment regimens should be noted in patients' files.

If participants find the treatment to be intolerable and wish to be cease taking the drug or if they are experiencing SAEs, clinicians may choose to allow those patients to cease the treatment regimen. Patients may also choose to withdraw from the study at any time of their choosing.

Concomitant Medications

All participants must discontinue use of anti-cancer therapies as per the guidelines written in section 3b: Inclusion Criteria, and patients should not be prescribed any other investigational therapies while enrolled in this trial (see section 3d: Co-Enrollment Guidelines). All concomitant medications taken by the participants must be reviewed and approved during the screening process. Prescribed and over-the-counter medications will be recorded at each visit in patients' files. Any medication prescribed for AEs throughout the course of this study will also be recorded on CRFs for each patient.

3h. Blinding

This study will be open-label for all participants and members of the treatment team will be unblinded. This is in keeping with previous unblinded phase I and II studies that have been conducted using elacestrant as compared to standard of care. Allowing patients and members of the treatment team to be unblinded will allow faster treatment in the case of an serious adverse event and ensures patients can make educated decisions regarding their future treatment and will allow an investigation of the safety of elacestrant while providing more flexibility for participants (Davey). This study will, however, be blinded for the evaluators who conduct the analyses.

3i. Informed Consent

Eligible subjects will only be included in the study after IRB/IEC approved informed consent form (ICF) has been signed. Informed consent will occur prior to any study procedures. The template ICF is included in Appendix B. The site specific ICF will be reviewed by sponsor prior to site initiation for enrollment.

4. Safety Considerations and Adverse Event Reporting

4a. Safety Monitoring

Protocol chairs, site investigators, and EC/DMC members will work together to monitor and ensure the safety of patients involved in this trial and respond to AEs/toxicity reports in a timely and reasonable fashion. Team members will determine a schedule to convene to respond to these reports, with additional calls occurring on the basis of necessity.

A safety analysis will also occur during the planned interim analysis, which occurs after roughly half the expected events have occurred in this study. See section 4b: Statistical Methods – Interim Analysis for more information. The trial will be stopped if the DMC determines there are an excess number of events in the intervention arm that would rule out the possibility of benefit or in the case of excess unacceptable AEs in the intervention arm that override any perceivable benefits of slowing cancer growth.

4b. Adverse Events

Adverse events (AEs) are defined as “unexpected medical problem[s] that happens during treatment with a drug or other therapy. Adverse events may be mild, moderate, or severe, and may be caused by something other than the drug or therapy being given” (“NCI Dictionary of Cancer Terms...”).

Study participants will be informed of all known side effects of the drugs they are given, but in the case of any AE that is not life-threatening, participants are instructed to contact their study clinician on a 24-hour phone number that will be provided upon entry into the study. If a life-threatening event is experienced, participants are instructed to seek immediate emergency care. If feasible, participants are encouraged to seek evaluation from their study clinician after such an event.

When given permission by the participants, any records from non-study providers related to care of AEs will be obtained, and pertinent information will be recorded in CRFs. Any participant who reports an AE will be followed-up with until they return to a baseline condition or they are stabilized.

All AEs, whether reported or observed, will be recorded regardless of the severity of the event or the potential relationship between treatment and the AE. All events will be graded using the National Cancer Institute’s Common Terminology Criteria for Adverse Events (NCI CTCAE version 5.0), which utilizes a grading scale for the severity of adverse events, ranging from grade 1 (mild or asymptomatic) to grade 5 (adverse event-related death) (“Common Terminology Criteria...”). Investigators will determine the relationship of AEs to treatment using clinical judgement and all known information about the treatment options.

4c. Serious Adverse Events

Serious adverse events (SAEs) are defined as per FDA guidelines ("What is..."). SAEs include any AE occurring at any dose of treatment that:

- Results in death
- Is life-threatening
- Leads to hospital admission (initial or prolonged)
    - Excludes admission due to cosmetic surgery, labor, or administrative/social admission
    - Excludes admissions for treatment of unrelated pre-existing conditions that have not increased in severity since the beginning of this trial
- Results in disability or permanent damage
- Is a congenital anomaly/birth defect
- Required intervention to prevent permanent damage or impairment
- Other serious medical events as determined by clinicians

Any medical event that may threaten the patient or may require some sort of intervention to prevent one of the above outcomes should similarly be treated as SAE.

4d. Adverse Event Reporting

AEs will be reported as per the guidelines in the *NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs* (NCI Guidelines for Investigators). Reporting is required for the agents elacestrant, as well as standard of care options fulvestrant, anastrozole, letrozole, and exemestane. The PI is ultimately in charge of AE reporting.

The CTEP-AERS Application will be used to electronically report AEs.

Expedited Reporting

Any suspected AE that is serious and unexpected must be reported immediately to the FDA. The expedited reporting period will be as is stated in the NCI Guidelines. These events must initially be reported within 24 hours, with a complete report within 5 calendar days of the initial report. All cases should follow the guidelines as laid out by the NCI.

5. Ethical Considerations

5a. Ethical Review

This protocol, the template of an informed consent form (see Appendix B), educational/ recruitment materials, and any adjustments will be reviewed and approved by the Protocol Committee, Data Monitoring Committee, and Ethics Committee to approve scientific content and compliance with research and human subject rules and regulations. Any other requested documents will also be reviewed and approved before usage.

The protocol should be reviewed by these committees at least once per year. These committees will receive efficacy and safety reports from investigators at least yearly, and within three months of the termination or completion of the study.

These reports will include updates on recruitment and retention, any changes in research activity, and any discernible problems involving risk to human participants. Review of study sites should also be included in these reports.

5b. Confidentiality

All data related to the study will be securely stored and managed at study sites. Printed participant information will be stored in locked cabinets away from open-access areas, such that only authorized individuals working on the trial are able to access these files. All electronic or laboratory data will be identified by a coded number in order to maintain confidentiality of patients, and databases will be password-secured and will store identifying data separate from other study data. These datasets will be linked by a coded ID number for each participant.

Except when required by the review committees or government/regulatory authorities, patient information will not be released without written permission from participants. This applies to patients at any study site.

5c. Specimen Storage and Possible Future Testing

Site staff will preserve blood samples collected at least through the end of the study. Participants will be asked to provide informed consent for these specimens to be stored past the end of the study or to be used at any time in future research testing. If participants do not consent for their specimens to remain in storage for future use, they will be destroyed once the study is completed or terminated.

5d. Study Discontinuation

The study may be discontinued at any time by the sponsor, the FDA, the treatment manufacturer, and/or site IRBs/ECs/DMCs. Discontinuation may happen due to many reasons, such as for benefit or futility, lagging recruitment, lack of funding, a similar study showing beneficial or futile results, etc. Study discontinuation is not considered lightly and is done in order to positively impact individual participants and the population of interest at large.

6. Statistical Analysis Plan

This section details the methods that will be used to address the study's primary and secondary objectives.

6a. Sample Size Calculation

The study aims to enroll 300 participants who meet the inclusion criteria, half in the elacestrant group and half in the placebo group. This will allow overall power of 80% to evaluate superiority of elacestrant over standard of care at an overall two-sided 5% significance level, if the difference between PFS on treatments is 2.5 months or greater, which has been determined to be of clinical relevance, assuming this population has a median PFS of 5 months. A two-sided significance level was chosen based on guidance from the fifth edition of *Fundamentals of Clinical Trials* (Friedman et al. 169).

6b. Statistical Methods

Descriptive Statistics

Baseline characteristics of each patient will be collected and displayed for all patients and stratified into each treatment group for comparison purposes. The below dummy table includes a list of information that will be collected.

Table 1: Baseline characteristics of study participants

Baseline measure		Treatment group (n=)	Standard of care group (n=)
Mean age in years (range)			
Race n (%)	AI/AN		
	Asian/NHPI		
	Black or African American		
	White		
	Other		
Ethnicity n (%)	Hispanic		

	Non-Hispanic		
Prior treatments	Mean number of prior treatments (range)		
	Prior chemotherapy, n (%)		
	Prior SERD, n (%)		
	Other treatments, n (%)		
Comorbidities, n (%)	Cardiovascular conditions		
	Hypertension		
	Diabetes		
	Rheumatologic disease		
	Hypothyroidism		
	Depression		

More comorbidities may be added; those above are the comorbidities that are known to be most associated with breast cancer in women (Sharma et al., Ng et al.).

Primary Analyses

Progression free survival probabilities within both treatment groups will be estimated using the Kaplan-Meier method at the 0.05 significance level. These Kaplan-Meier curves and 95% confidence intervals for each treatment group will be presented graphically. The hazard ratio and its 95% confidence interval will be estimated using the Cox proportional hazards model, with adjustment for patients' baseline characteristics and prior treatment.

The Cox proportional hazards model depends on the assumption of proportional hazards; the appropriateness of this assumption will be evaluated graphically and by checking the scaled Schoenfeld residuals of the model. If the proportional hazards assumption is not met, stratification will be employed for covariates that violate this assumption.

Secondary Analyses

Overall survival will be analyzed similarly to progression free survival, using Kaplan-Meier curves with the endpoint being death. Duration of response will also be analyzed similarly, using time until tumor progression as the outcome.

Safety and tolerability measures will be analyzed using the NCI CTCAE version 5.0 as described in section 4b: Adverse Events ("Common Terminology Criteria..."). This resource utilizes a grading scale for the severity of adverse events, ranging from 1 to 5. The highest

grade per patient will be used, and a t-test will be conducted to compare those on elacestrant to standard of care.

Patients' quality of life measures are also of interest. For each patient, the average number of minutes of sleep per day will be calculated throughout the study, then baseline measurements will be compared to measurements at the end of the study for each patient. Change scores for patients on both arms will be compared using t-tests. The average amount of physical activity participants engaged in per day throughout the course of the study will also be calculated and compared across both study arms similarly to sleep data. An interim analysis of quality of life measures may be performed concurrently with the interim analysis for the primary objective. The results from these analyses should be used as hypothesis generating due to the repeated number of testing that will be done using the same data.

Quality of life data will also be collected using questionnaires at each follow-up visit. Overall health scores will be calculated at each visit, and these scores at baseline will be compared with scores at the end of the study for each patient, and changes across both arms will ultimately be compared similarly to objective quality of life data.

Subgroup Analyses

Progression free survival will be reported for each level of the stratification factor (SERD, Y vs N) and baseline characteristics described in Table 1 to check the homogeneity of treatment effect across levels of factors. Median values for each level of factors will be computed using Kaplan-Meier estimates. Cox proportional hazards model will be used to calculate hazard ratios and 95% CIs. Forest plots will be generated to display hazard ratio treatment differences across subgroups. Similar subgroup analyses will also be performed for a key secondary endpoint, overall survival (OS). If a level of a factor consists of fewer than 5% of randomized patients, analysis within that level will be omitted.

Handling of Missing Data

Situation	Date of PD/Death or Censoring	PFS outcome
Documented Progressive Disease (PD) as determined by investigator	Date of earliest sign of PD	Progressed
Death before the first post-baseline disease assessment or between adequate tumor assessment visits	Date of death	Death

No PD as determined by investigator or death at completion or termination of study	Date of study completion or termination	Censored
Lost to follow-up after >= 2 missed consecutive disease assessments	Date of last progression-free disease assessment prior to missed assessments or later	Imputed
Initiation of alternative anticancer therapy	Date of last progression-free disease assessment prior to initiation of other anticancer therapy	Censored for Sensitivity Analyses
No tumor assessment at baseline or post-baseline	Date of randomization	Censored

The date of disease progression, death, or censoring will be recorded to the nearest day as accurately as possible. Because median PFS is relatively short for the population of interest, this is imperative to ensure the integrity of the trial.

All patients in the intent-to-treat population will be included in analyses, whether the primary endpoint was observed during the trial for that individual or censored, and whether or not patients adhered to treatment. The only reason a patient will be excluded from analyses is if they dropped out prior to randomization. However, if a patient is randomized to a treatment arm and drops out before taking medication, they will still be included in analyses, as this may have been due to treatment assignment. All effort will be made to reach patients that do not attend follow-ups in order to determine their status, and an attempt will be made to confirm the status of all patients still in the study at the end of the two years. However, if this information cannot be determined, data will be assumed as Missing Not At Random (MNAR) in order to be conservative, and status at each follow-up time will be calculated through multiple imputation using a mixed model with a logistic link.

If patients drop out of the study but do not initiate the withdrawal of their consent (WC), follow-up will still be conducted to determine patients' vital status at the minimum. For those patients who do initiate WC, outcomes will be censored at time of withdrawal.

Interim Analyses

An interim analysis of the primary endpoint will be conducted after half the expected events have occurred. All results will be reviewed by an independent Data Monitoring Committee (DMC). The DMC may recommend that the trial be discontinued for benefit or futility, or for

potential changes to the protocol for safety reasons. The O'Brien-Fleming alpha spending method will be used to determine the alpha allocation for this interim PFS analysis in order to allow for a small loss in alpha at the final analysis.

Multiplicity

For exploratory outcomes, there are no planned adjustments of Type I error, as those analyses are intended to be hypothesis generating, not confirmatory. The O'Brien-Fleming alpha spending method is utilized for primary and secondary analyses.

7. **Facilities, Resources, and Equipment**

7a. Facilities

There will be 30 total sites involved in this study. Each site will complete a feasibility site questionnaire to determine appropriate resources and patient populations to conduct the study. Research facilities must have secure location to store research supplies, including temperature controlled, locked, limited access storage for the investigational product. Site must have appropriate infrastructure to conduct recommended tests and procedures as a part of the standard of care in treating patients with HR+, HER2- metastatic breast cancer.

Statistical analyses for primary, secondary, and exploratory endpoints will be conducted by statisticians at the University of Washington (UW) using UW facilities and equipment. Lab work and imaging analyses will be done on-site when possible and off-site when necessary by trained laboratory technicians.

7b. Resources

The best resources for this clinical trial should be those employed to work on the trial. Physicians and providers are expected to have experience conducting randomized drug trials in this study population (or a similar population). Sufficient research site staff must be employed to maintain research records, and to support study screening and recruitment. Research pharmacy staff must be properly educated on the effects of elacestrant and standard of care treatments and ensure adherence to study protocols when dispensing medication to participants.

Because trust between public health officials and communities is of the utmost importance, a website dedicating to informing the public of this clinical trial and any results will be maintained and updated regularly. Sites will also have access to pamphlets with more information for

participants and must be prepared with informed consent forms and CRFs, as well as any other documents noted in the protocol.

7c. Equipment

Sites will require working MRI and CT machines so that patients can undergo imaging procedures to evaluate cancer progression. Additionally, each site and data manager will need a secure laptop for data collection, management, and analysis purposes. All data will be de-identified and reliably stored, as further explained in section 3e: Data Capture.

Each patient will be provided with either elacestrant tablets monthly or standard of care treatment as required by their clinician. Equipment needed to administer treatment (pill bottles, labels, injection needles, etc.) must be available to be utilized at sites. Every individual will also be given a smartwatch that has the capabilities of tracking quality of life measures.

8. Organization and Administration

Due to the global nature of this study, initial regulatory submission of the protocol and associated registration documents will be submitted to the respective regulatory authorities by the trial oversight team. Thereafter, each research site, under the oversight of the investigator, will be responsible for submitting the protocol, including any subsequent amendments to their institutional review board (IRB)/ethics committee (EC), according to local requirements. Each site will also submit any patient-facing material, including the informed consent form and recruitment/retention material to their IRB/EC. Investigators are responsible for ensuring any additional IRB/EC required documents are submitted, in alignment with their local guidelines.

Regulatory approval along with IRB/EC approval of the investigator, protocol, and informed consent form must be obtained prior to the first patient visit. Patient facing material must be approved by the IRB/EC prior to use with any patient.

Study Monitoring will be performed by a trial-oversight team selected CRO. Investigators are expected to permit study monitors to inspect study facilities, as necessary to support their assessment of quality assurance and data integrity.

The investigator will maintain and securely store complete, accurate, and current study records throughout the study. This documentation will be retained until communicated by the trial oversight team as no longer required, in alignment with federal, regulatory requirements.

Safety monitoring by the trial oversight team will be coordinated by the medical director. This monitoring will include a review of adverse events trends and laboratory abnormalities. Furthermore, an independent Data Monitoring Committee (DMC), consisting of at least 1 clinician and 1 statistician, will oversee interim analyses for safety and efficacy. The DMC recommendations will be communicated to the trial oversight team medical director and co-lead biostatisticians.

9. Budget

This proposed budget is expected to cover three years of the study and assumes all patients are recruited within year one of the study, allowing each patient to remain on treatment for two years regardless of when they were recruited during year one. Years two and three are adjusted for inflation. Sources and justification of many of these costs can be found in the below section 9d: Budget Justification.

9a. Year 1 Costs

Title		Quantity	Cost per Unit	Total Cost
Scientist and Senior Personnel Salaries				
	Medical Director	1 x 1.0	200,000	200,000
	Site Principal Investigator	30	125 (per visit)	75,000
	Study Coordinator	30 x 0.25	65,000	487,500
	Recruitment Coordinator	1 x 1.0	60,000	60,000
	Lead Statistician	1 x 0.25	115,000	28,750
Other Personnel Salaries				
	Staff Physician/Nurse	30 x 0.25	80,000	600,000
	Lab Technician	30 x 0.1	50,000	150,000
	Data Manager	30 x 0.25	100,000	750,000
	Junior Statistician	1 x 0.25	85,000	21,250
Recruitment Processes				
	Website creation and maintenance	1	3,500	3,500
	Postcard mailer creation, printing, and sending	1,000	2 (+100 for design)	2,100

	Flyer and pamphlet creation and printing	1,000	5 (+200 for design)	5,200
	Poster creation and printing	50	35 (+500 for design)	2,250
	Advertisements (television, radio, and social media)	50	500	25,000
	Medical record pulls	500	10	5,000
	Patient screening	200	250	50,000
	Informed consent	100	120	12,000
	Randomization	100	75	7,500
	Baseline visit	100	600	60,000
Equipment purchase				
	Laptops	30	600	18,000
	Smartwatches	100	250	25,000
Supplies				
	Drug manufacturing and safety	1	350,000	350,000
	Drug labels and packaging	1,200	1	1,200
	Collection of unused drugs	30	300	9,000
	CT imaging	300	1,000	300,000
	PK sampling/nonroutine labs	600	1,000	600,000
Domestic travel				
	Training	10	2,500	25,000
	Conferences	2	2,500	5,000
	Patient travel/parking reimbursement	600	50	30,000
Alterations and Renovations				
	Hiring due to turnover	60	4000	240,000
	Training of new employees	60	1000	60,000
	Necessary technological replacements/upgrades	50	Varies	100,000
	Withdrawal from study	5	100	500
Other Direct Costs				
	Document translation	5	250	1,250

	Follow-up visits	300	1,000	300,000
	Site start-up	30	4,000	120,000
	AE review	100	75	7,500
	Site reviews	30	1,000	30,000
	CRF system licensing	1	48,000	48,000
	Document storage	1	1,000	1,000
	CRO	1	60,000	60,000
Overhead costs				
	50% of salaries			1,186,250
Total Costs				4,876,500

9b. Year 2 Costs

Title		Quantity	Cost per Unit	Total Cost
Scientist and Senior Personnel Salaries				
	Medical Director	1 x 1.0	210,000	210,000
	Site Principal Investigator	30	135 (per visit)	247,860
	Study Coordinator	30 x 0.25	68,250	511,875
	Recruitment Coordinator	1 x 1.0	63,000	63,000
	Lead Statistician	1 x 0.25	120,750	30,188
Other Personnel Salaries				
	Staff Physician/Nurse	30 x 0.25	84,000	630,000
	Lab Technician	30 x 0.1	52,500	157,500
	Data Manager	30 x 0.25	105,000	787,500
	Junior Statistician	1 x 0.25	89,250	22,313
Recruitment Processes				
	Website maintenance	1	3,570	3,570
	Postcard mailer printing and sending	500	1	500
	Advertisements (television, radio, and social media)	50	510	25,500
	Patient screening	400	255	102,000
	Informed consent	200	122	24,400
	Randomization	200	77	15,400

	Baseline visit	200	612	122,400
Equipment purchase				
	Smartwatches	200	255	51,000
Supplies				
	Drug manufacturing and safety	1	357,000	357,000
	Drug label and packaging	3,600	1	3,600
	Collection of unused drugs	30	306	9,180
	CT imaging	900	1,020	918,000
	PK sampling/nonroutine labs	1,800	1,020	1,836,000
Domestic travel				
	Training	10	2,550	25,500
	Conferences	2	2,550	5,100
	Patient travel/parking reimbursement	3,600	50	91,800
Alterations and Renovations				
	Hiring due to turnover	60	4080	244,800
	Training of new employees	60	1020	61,200
	Necessary technological replacements/upgrades	50	Varies	102,000
	Reconsent	300	40	12,000
	Withdrawal from study	10	102	1,020
Other Direct Costs				
	Follow-up visits	900	1,020	918,000
	AE review	300	77	23,100
	Site reviews	30	1,020	30,600
	CRF system licensing	1	48,960	48,960
	Document storage	1	1,020	1,020
	CRO	1	61,200	61,200
Overhead costs				
	50% of salaries			1,330,118
Total costs				7,755,085

9c. Year 3 Costs

Title		Quantity	Cost per Unit	Total Cost
Scientist and Senior Personnel Salaries				
	Medical Director	1 x 1.0	220,500	220,500
	Site Principal Investigator	30	150 (per visit)	280,908
	Study Coordinator	30 x 0.25	71,663	537,473
	Recruitment Coordinator	1 x 1.0	66,150	66,150
	Lead Statistician	1 x 0.25	126,788	31,697
Other Personnel Salaries				
	Staff Physician/Nurse	30 x 0.25	88,200	661,500
	Lab Technician	30 x 0.1	55,125	165,375
	Data Manager	30 x 0.25	110,250	826,875
	Junior Statistician	1 x 0.25	93,713	23,428
Recruitment Processes				
	Website maintenance	1	3,641	3,641
Supplies				
	Drug manufacturing and safety	1	364,140	364,140
	Drug label and packaging	3,600	1	3,600
	Collection of unused drugs	30	312	9,360
	CT imaging	900	1,040	936,360
	PK sampling/nonroutine labs	1,800	1,040	1,872,720
Domestic travel				
	Training	10	2,600	26,000
	Conferences	2	2,600	5,200
	Patient travel/parking reimbursement	1800	50	90,000
Alterations and Renovations				
	Hiring due to turnover	60	4,162	249,720
	Training of new employees	60	1,040	62,400
	Necessary technological replacements/upgrades	50	Varies	104,040
	Reconsent	300	41	12,300
	Withdrawal from study	10	102	1,020
Publication Costs				

	Report generation	1	1,000	1,000
	Article processing charge	1	3,000	3,000
Other Direct Costs				
	Follow-up visits	900	1,040	936,000
	AE review	300	79	23,700
	Site reviews	30	1,040	31,200
	Site close-out	30	1,000	30,000
	CRF system licensing	1	49,940	49,940
	Document storage/archiving	1	1,040	1,040
	CRO	1	62,424	62,424
Overhead costs				
	50% of salaries			1,406,953
Total costs				7,692,711

9d. Budget Justification

The year one budget is based on current market prices, with years two and three adjusted for inflation, with the assumption that salaries will increase by approximately 5% per year and goods and services will approximately increases in cost by 2%. All calculations are made with the expectation that standard of care procedures will be covered by insurance, as is standard.

Salaries

All salary data is consistent with median salaries for these positions in the United States. There is a need for a head recruitment coordinator as well as site-specific study coordinators; often study coordinators are tasked with recruitment, but this extra job is time-consuming and is better led by another person who is able to ensure recruitment goals are being met at all sites.

Recruitment

Recruitment costs are justified by the need to employ multiple avenues for recruitment. Because hitting recruitment goals in a timely manner is important for the integrity of the trial – as the most up-to-date information and treatment advances must be employed in the pursuit of scientific advancements – it is imperative that multiple methods are utilized in recruiting patients near each site. Additionally, it is expected that approximately 5% of eligible patients will enroll and that roughly 50% of patients do not move past the screening phase, meaning a wide net must

be cast to reach those who desire to take part in a clinical trial (Unger et al, Mahajan et al.). Refer to the section 3a: Recruitment for more information.

Equipment Purchase

The cost of smartwatches is justifiable for this study: while the primary goal of this clinical trial is to determine the efficacy of elacestrant, it would be unethical, both at the individual and population-wide level, to ignore the safety and quality of life measurements of patients. These smartwatches allow investigators to collect information from patients without the need for patients to come in for extra appointments and fill out further surveys. Laptop purchases are also essential: for confidential data management, individuals must not use personal laptops for analyses.

Supplies

Drug manufacturing and safety checks are essential for the health of study individuals are to maintain the clinical trial. Costs for manufacturing and safety as estimated based on guidance from the Head Of Clinical Operations at the CRO Sofpromed (Ledesma). However, there will never be 100% adherence to any treatment. As such, trial sites will collect unused drugs from patients for safe disposal. This trial also budgets for nonroutine labs, which will not be covered through standard of care, but are essential in ensuring drug safety and efficacy.

Travel

Training sessions are necessary so that all clinical trials staff can tend to patients with the highest level of care and understanding. Conference attendance is similarly essential in order to share and maintain a level of knowledge about cutting edge research and tools.

A $50 travel reimbursement for patients for each visit will cover gas prices and parking costs at each site, which allows for ease of transportation for patients who are already stressed and helps to ensure that patients do not drop out of the study due to monetary restraints or undue stress put upon them due to travel.

Alterations and Renovations

It is expected that there will be roughly 30% turnover among clinical trial employees, and as such hiring and training costs are accounted for (Studna). Additionally, it is prudent to replace or upgrade aging technology, as the findings of the trial depend on the usage of laptops,

smartwatches, etc. There may also be a need to reconsent participants based on interim findings and/or recommendations of the DMC, and as such, this is included in alterations costs.

Publication Costs

Publication costs are based on charges listed by JAMA Network; however, costs will vary between journals (“Why Publish...”). It is imperative to publish findings of this trial, whether they are positive or negative, so that public health professionals can learn from these results.

Other Costs

Each site needs to be reviewed by independent reviewers in order to ensure operations are commencing smoothly and data is captured accurately, and AEs/SAEs need to be reviewed throughout the course of the study for the safety of participants. It is also necessary to collect, store, and archive data safely and confidentially so that it can be used only for its intended purposes.

References

"Assessing Participant Adherence during Clinical Trials." *EUPATI Toolbox*, EUPATI, 18 Nov. 2016, https://toolbox.eupati.eu/resources/assessing-participant-adherence-during-clinical-trials/.

Bardia, Aditya, et al. "Phase I Study of Elacestrant (RAD1901), a Novel Selective Estrogen Receptor Degrader, in ER-Positive, HER2-Negative Advanced Breast Cancer." *Journal of Clinical Oncology*, 29 Jan. 2021, https://ascopubs.org/doi/full/10.1200/JCO.20.02272.

Bihani, Teeru, et al. "Elacestrant (RAD1901), a Selective Estrogen Receptor Degrader (SERD), Has Antitumor Activity in Multiple ER+ Breast Cancer Patient-Derived Xenograft Models." *American Association for Cancer Research*, American Association for Cancer Research, 14 Aug. 2017, https://aacrjournals.org/clincancerres/article/23/16/4793/79974/Elacestrant-RAD1901-a-Selective-Estrogen-Receptor.

"Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0." *National Cancer Institute*, U.S. Department of Health and Human Services, 27 Nov. 2017, https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

Davey, Reginald. "What Is an Open-Label Clinical Trial?" *News Medical*, 31 Mar. 2022, https://www.news-medical.net/life-sciences/What-is-an-Open-Label-Clinical-Trial.aspx#:~:text=Open%2Dlabel%20trials%20can%20be,specific%20protocols%20of%20their%20own.

Diéras, Véronique, et al. "Long-Term Pooled Safety Analysis of Palbociclib in Combination with Endocrine Therapy for HR+/HER2- Advanced Breast Cancer." *Journal of the National Cancer Institute*, Oxford University Press, 18 July 2018, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6449170/.

Friedman, Lawrence M., et al. *Fundamentals of Clinical Trials*. 5th ed., Springer International Publishing, 2015.

Goetz, Matthew P, et al. "Safety and Efficacy of Abemaciclib plus Endocrine Therapy in Older Patients with Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: An Age-Specific Subgroup Analysis of Monarch 2 and 3 Trials." *National Library of Medicine*, Breast Cancer Research and Treatment, 3 Jan. 2021, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7990838/.

Ledesma, Patricio. "How Much Does It Cost to Manufacture a Drug for a Clinical Trial?" *Sofpromed*, Sofpromed, 13 Dec. 2020, https://www.sofpromed.com/how-much-does-it-cost-to-manufacture-a-drug-for-a-clinical-trial.

Li, Jinming, et al. “Association of Cyclin-Dependent Kinases 4 and 6 Inhibitors With Survival in Patients With Hormone Receptor-Positive Metastatic Breast Cancer.” *JAMA Network Open*, American Medical Association, 13 Oct. 2020, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8094425/.

Loibl, Sibylle, et al. *Breast Cancer*. The Lancet, 1 Apr. 2021, https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32381-3/fulltext.

Mahajan, P, et al. “Reasons Why Patients Fail Screening in Indian Breast Cancer Trials.” *Perspectives in Clinical Research*, Medknow Publications & Media Pvt Ltd, 2015, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4640011/#:~:text=The%20overall%20screen%20failure%20rate,from%20breast%20cancer%20was%2056.1%25.

Myles, Paul S, et al. “Ethical and Scientific Considerations for Patient Enrollment into Concurrent Clinical Trials.” *Trials*, BioMed Central, 29 Nov. 2014, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4258295/#:~:text=Safety%20considerations,the%20co-enrolled%20study%20participants.

“NCI Dictionary of Cancer Terms: Adverse Events.” *National Cancer Institute*, https://www.cancer.gov/publications/dictionaries/cancer-terms/def/adverse-event.

“NCI Guidelines for Investigators – Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs.” *Adverse Event Guidelines*, National Cancer Institute, 16 Sept. 2013, https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/aeguidelines.pdf.

Ng, Huah Shin, et al. “Patterns of Comorbidities in Women with Breast Cancer: A Canadian Population-Based Study.” *Cancer Causes & Control: CCC*, U.S. National Library of Medicine, 6 July 2019, https://pubmed.ncbi.nlm.nih.gov/31280456/.

Raschi, Emanuel, et al. “Thromboembolic Events with Cyclin-Dependent Kinase 4/6 Inhibitors in the FDA Adverse Event Reporting System.” *Cancers*, MDPI, 7 Apr. 2021, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8067683/.

“Sample UK English EQ-5D-5L.” *EuroQol Research Foundation*, EuroQol Research Foundation, 2009, https://euroqol.org/eq-5d-instruments/sample-demo/.

Sharma, Neeti, et al. “Association of Comorbidities with Breast Cancer: An Observational Study.” *Tropical Journal of Medical Research*, 6 Dec. 2016, https://scholar.harvard.edu/narender/publications/association-comorbidities-breast-cancer-observational-

study#:~:text=The%20most%20prevalent%20comorbidities%20associated,around%2075%25%20of%20the%20cases.

Studna, Andy. “Turnover for Clinical Monitoring Remains High.” *Applied Clinical Trials Online*, Applied Clinical Trials Online, 15 Apr. 2021, https://www.appliedclinicaltrialsonline.com/view/turnover-for-clinical-monitoring-remains-high.

Tripathy, D, et al. “Pooled Safety Analysis of First-Line Ribociclib (RIB) plus Endocrine Therapy (ET) in HR+/HER2– Advanced Breast Cancer (ABC).” *Annals of Oncology*, 1 May 2019, https://www.annalsofoncology.org/article/S0923-7534(19)30434-X/fulltext.

Unger, Joseph et al. “The Role of Clinical Trial Participation in Cancer Research: Barriers, Evidence, and Strategies.” *American Society of Clinical Oncology Educational Book*, 19 May 2016, https://ascopubs.org/doi/10.1200/EDBK_156686#:~:text=Fewer%20than%20one%20in%2020,not%20changed%20substantially%20over%20time.

Waks, Adrienne G and Eric P Winer. “Breast Cancer Treatment.” Edited by Eric P Winer, *JAMA*, JAMA Network, 22 Jan. 2019, https://jamanetwork.com/journals/jama/article-abstract/2721183.

West, Malinda T, et al. “CDK 4/6 Inhibitors Are Associated with a High Incidence of Thrombotic Events in Women with Breast Cancer in Real-World Practice.” *European Journal of Haematology*, U.S. National Library of Medicine, 18 Feb. 2021, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8087188/.

“What Is a Serious Adverse Event?” *U.S. Food and Drug Administration*, FDA, 1 Feb. 2016, https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event.

“Why Publish in JAMA Network Open?” *JAMA Network Open*, JAMA Network Open, Feb. 2022, https://jamanetwork.com/journals/jamanetworkopen/pages/for-authors#:~:text=JAMA%20Network%20Open%20is%20published,charge%20(APC)%20of%20%243000.

Appendices

Appendix A: Study Calendar

Period	Screening/ Enrollment Day -28 to -1	Baseline Day 1	Treatment		End of Treatment	FU
Visit Day/Week Procedure	1	2 Day 1	3-8 Every 2 months (± 1 week) until year 1	9-16 Every 3 months (± 2 weeks) until EOT	EOT	Every 3 months until end of year 3
Informed Consent	X[a]					
Symptom Assessment	X	X	X	X	X	
Physical Exam	X	X	X	X	X	
Performance Status	X	X	X	X	X	
LFTs/ CBC w/ diff	X	X	X	X	X	
CT CAP	X	X	X	X	X	
Bone Scan	X		X[b]	X	X	
QoL Assessment		X	X	X	X	
Study Drug dispensation		X	X	X		
Pill Diary Assessment			X	X	X	
Research Blood Specimens	X	X	X	X	X	
Survival Assessment						X

[a] or at any visit where reconsenting is necessary [b]Bone scan on visits 4, 6, 8, 14, and 16 during treatment phase

Appendix B: Template Informed Consent

Study Title for Participants: Testing of an oral steroidal estrogen receptor degrader, Elacestrant, compared to the usual approach for metastatic breast cancer.

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: A Multi-Center, Randomized, Open-Label, Phase 2b Study of Elacestrant versus Standard of Care in Patients with Estrogen Receptor Positive, HER2 Negative Metastatic Breast Cancer

Researchers: [List names, academic/staff positions, division/departments, telephone number of lead researcher (PI) of site)

24-hour emergency telephone number: [name or position and phone number]

Overview and Key Information

You are being asked to be in a medical research study. This form is designed to tell you everything you need to think about before you decide if you want to be a part of the study. It is entirely your choice. If you decide to take part, you can change your mind later on and withdraw from the research study. The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you. Before making your decision:
Please carefully read this form or have it read to you
Please listen to the study doctor or study staff explain the study to you
Please ask questions about anything that is not clear. You can take a copy of this consent form, to keep. Feel free to take your time thinking about whether you would like to participate. You may wish to discuss your decision with family or friends. Do not sign this consent form unless you have had a chance to ask questions and get answers that make sense to you. By signing this form you will not give up any legal rights.
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This Web site will not include information that can identify you. At most the Web site will include a summary of the results. You can search this Web site at any time.

What am I being asked to do?

We are asking you to take part in this research study because you have breast cancer that has spread outside your breast, and your cancer has Estrogen Receptors present.

Taking part in this study is your choice.

You can choose to take part or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

Why is this study being done?

This study is being done to answer the following question:

Can we extend the length of time before your breast cancer grows or spreads by using Elacestrant instead of the usual drugs?

We are doing this study because we want to find out if this approach is better or worse than the usual approach for your metastatic breast cancer. The usual approach is defined as care most people get for metastatic breast cancer.

What is the usual approach to my metastatic breast cancer?

The usual approach for patients who are not in a study is treatment with FDA-approved hormonal drugs that impact estrogen receptors; such as fulvestrant, anastrozole, letrozole, or exemestane. If the hormonal drugs stop working against your cancer, then doctors may use other drugs or chemotherapy.

What are my choices if I decide not to take part in this study?

- You may choose to have the usual approach described above.
- You may choose to take part in a different research study, if one is available.
- You may choose not to be treated for cancer.
- You may choose to only get comfort care to help relieve your symptoms and not get treated for your cancer.

What will happen if I decide to take part in this study?

If you decide to take part in this study, you will either get the study drug, Elacestrant, until your disease gets worse or the side effects become too severe or you will get the usual approach for your cancer as described above until your disease gets worse or the side effects become too severe.

After you finish the study drug, Elacestrant, or this line of usual therapy, your doctor will continue to follow your condition as a part of the study for every 3-months for 2 years and then annually for a total of 10-years to watch you for side effects and overall survival. Your doctor may want to see you more often than required for the study.

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.

If you choose to take part in this study, there is a risk that the study drug, Elacestrant may not be as good as the usual approach for your cancer in preventing your cancer from getting worse.

There is also a risk that you could have side effects from the study drug, Elacestrant. These side effects may be worse and may be different than you would get with the usual approach for your cancer.

There may be some risks that the study doctors do not yet know about.

Benefits

There is evidence that Elacestrant is effective in slowing the spread of your type of cancer. It is not possible to know now if the study drug will extend your time without your disease from spreading compared to the usual approach. This study will help the study doctors learn things that will help people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- For women: You become pregnant while on the study.
- The study is stopped by the Data Safety Monitoring Committee, Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor. The study sponsor is the organization who oversees the study.

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

What is the purpose of this study?

The purpose of this study is to compare the usual treatment alone to using Elacestrant. But, it could also cause side effects, which are described in the risks section below.

This study will help the study doctors find out if this different approach is better than the usual approach. To decide if it is better, the study doctors will be looking to see if Elacestrant increases the time to cancer progression of participants by 2.5 months compared to the usual approach.

What are the study groups?

This study has 2 study groups. You will not be told which group you are in.

- **Group 1**

  If you are in this group, you will get the usual hormone therapy used to treat this type of cancer, there are a couple different FDA-approved options and which one is best for you will be decided on between you and your doctor. You will get this drug until your disease gets worse or the side effects become too severe See the study calendar for more information.

  There will be about 150 people in this group.

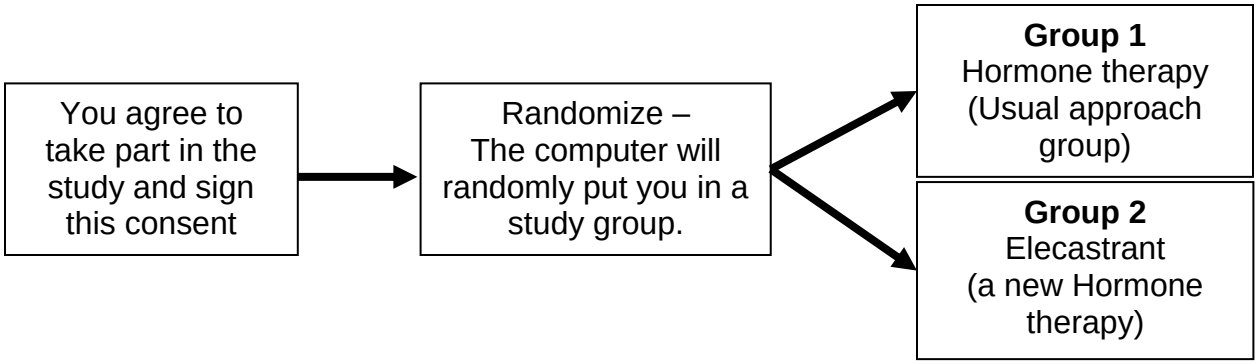
- **Group 2**

  If you are in this group, you will get the study drug, Elacestrant. Elacestrant is taken by mouth every day until your disease gets worse or the side effects become too severe. See the study calendar for more information.

  There will be about 150 people in this group.

We will use a computer to assign you to one of the study groups. This process is called "randomization." It means that your doctor will not choose and you cannot choose which study group you are in. You will be put into a group by chance. You will have an equal chance of being in Group 1 or Group 2.

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



What exams, tests, and procedures are involved in this study?
Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

This will include:

- Physical exams and symptom assessment
- Laboratory testing (complete blood count and liver function tests)
- Computer tomography (CT scan)
- Bone Scan

You will need to have research blood samples taken for the study. You and your study doctor will not get the results of this blood specimen testing. Additionally, you will be asked to complete questionnaires about your health and to complete a pill diary for research purposes.

What risks can I expect from taking part in this study?

General Risks
If you choose to take part in this study, there is a risk that the study drug may not be as good as the usual approach for your cancer at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The study drug used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use during the study and for 6 months after you have completed the study.

Side Effect Risks

The study drug, Elacestrant, used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and let you know if changes occur that may affect your health.

There is also a risk that you could have other side effects from the study drug(s), Elacestrant / the usual therapy.

Here are important things to know about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

What are my responsibilities in this study?

If you choose to take part in this study you will need to:

- Keep your study appointments.
- Tell your doctor about:
    - all medications and supplements you are taking
    - any side effects
    - any doctors' visits or hospital stays outside of this study
    - if you have been or are currently in another research study.
- Write down in your medication diary when you take the study drug at home.

For women: Do not get pregnant or breastfeed while taking part in this study. Tell your study doctor right away if you think that you or your partner have become pregnant during the study or within 6 months after your last dose of study drug.

What are the costs of taking part in this study?

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the study, just as you would if you were getting the usual care for your metastatic breast cancer. This includes:

- the costs of tests, exams, procedures, and drugs that you get during the study to monitor your safety, and prevent and treat side effects.
- the costs of getting the usual therapy approach if randomized to group 1.
- your insurance co-pays and deductibles.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

You and/or your insurance provider will not have to pay for exams, tests, and procedures done for research purposes only or that are covered by the study.

You will be paid for travel costs for study visits while taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What happens if I am injured because I took part in this study?

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.
Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information.

Where can I get more information?

You may visit the NCI web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor (*insert name of study doctor[s]*) at (*insert telephone number, and email address if appropriate*).

For questions about your rights while in this study, call the (*insert name of organization or center*) Institutional Review Board at (*insert telephone number*).

My signature agreeing to take part in the study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study. I also agree to take part in any additional studies where I circled "yes".

Participant's signature _____

Date of signature _____

Signature of person conducting the informed consent discussion _____

Date of signature _____

Appendix C: Euro-Qol-5 Dimension-5 Level (EQ-5D-5L) (“Sample UK...”)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐