PROTOCOL NUMBER:	**16-1042**
PROJECT TITLE:	**Randomized Phase II trial of preoperative fulvestrant with or without enzalutamide in ER+/Her2- breast cancer**
VERSION DATE:	**1/5/2023**
LEAD PRINCIPAL INVESTIGATOR:	**Anthony Elias, MD**
COORDINATING CENTER:	**University of Colorado** **Anschutz Medical Campus** **Division of Medical Oncology** **12801 E. 17th Avenue** **Mailstop 8117** **Aurora, CO 80045** **anthony.elias@cuanschutz.edu**
PARTICIPATING SITES:	**Multiple centers**
IND:	**Exempt**
FUNDING SUPPORT / STUDY REFERENCE NUMBER:	**Department of Defense (DOD)** **W81XWH-13-1-0091**
ASTELLAS REFERENCE NUMBER:	**ENZA16F06**

STATEMENT OF COMPLIANCE

This is an investigator-initiated study. The lead principal investigator (PI), **Anthony Elias, MD**, is conducting the study and acting as the sponsor. As the sponsor-investigator, both the legal/ethical obligations of a PI and those of a sponsor will be followed.

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by applicable United States (US) laws and applications, including but not limited to United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

The PI will assure that no changes to the protocol will take place without documented approval from the Institutional Review Board (IRB). All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Sponsor-Lead Principal Investigator: Anthony Elias, MD

Print/Type Name

Signed: _____ **Date:** _____

Signature

Site Principal Investigator: _____

Print/Type Name

Signed: _____ **Date:** _____

Signature

PARTICIPATING SITES

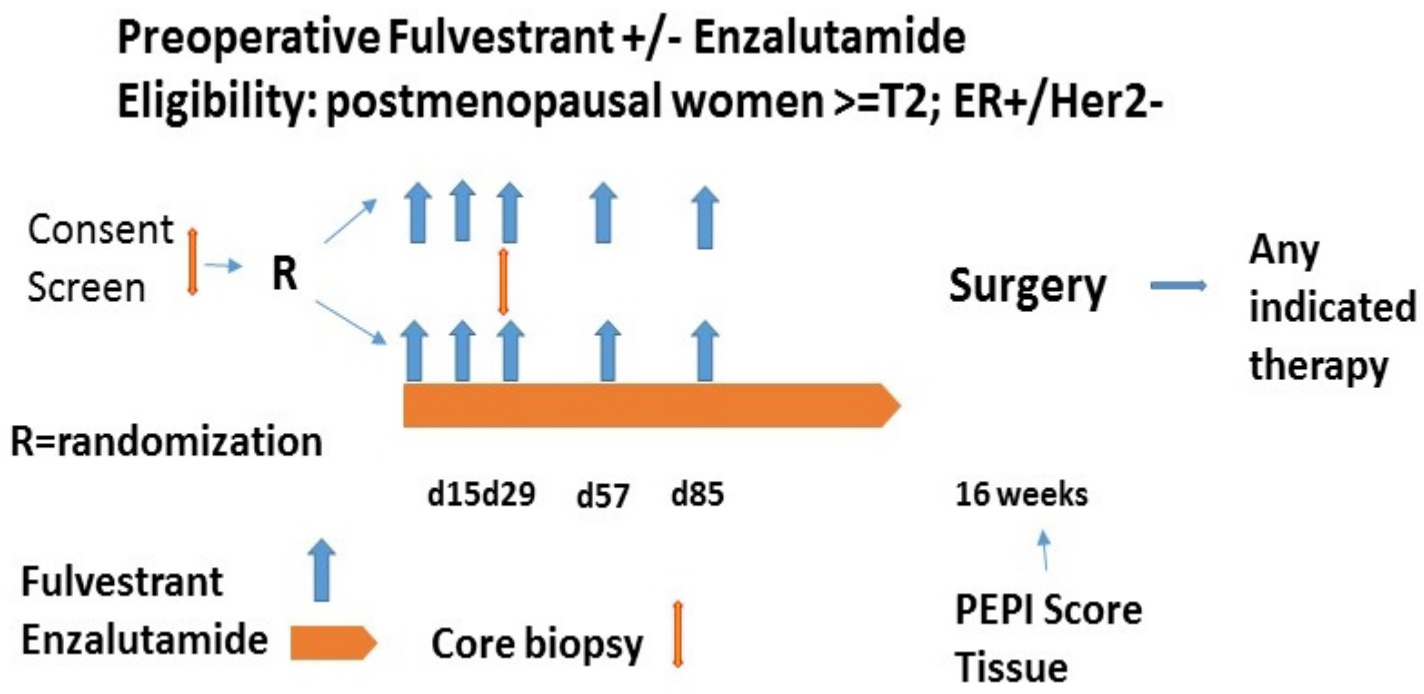
A complete and current listing of investigators, research personnel, research facilities and other study centers participating in this study will be maintained throughout the duration of this study on a **Protocol Contact List** form, incorporated herein by reference.

PROTOCOL / TRIAL SUMMARY

Protocol Title:	**Randomized Phase II trial of preoperative fulvestrant with or without enzalutamide in ER+/Her2- breast cancer**
Protocol Number:	16-1042
Trial Phase:	II
Objectives:	**Primary Objective:** Evaluate the rate of PEPI score equal to 0 at 16 weeks post treatment for each of the two treatment arms separately. **Secondary Objectives:** 1. To determine the percentage of progression-free survival (PFS) andclinical response rate (by physical exam and breast imaging after 16 weeks of therapy prior to surgery for the single drug arm and combination of enzalutamide/fulvestrant arm separately. 2. To assess the association between PEPI score and the clinical outcomes such as PFS, response ratesfor all the subjects. 3. To confirm the safety profile of the combination. 4. To determine the extent of AR expression and signaling in breast tissue, to evaluate the effect of the drug (s) on the tumor, and to evaluate the relationship of these effects on clinical outcomes for the two arms separately.
Endpoint(s):	The preoperative endocrine prognostic index (PEPI) was developed from the P024 trial and validated in the IMPACT trial (22). PEPI is a model that combines ER, pathologic tumor site, nodal status, and Ki67 score at time of surgery to predict subsequent risk of recurrence. Those patients with a low PEPI score of 0 are unlikely to benefit from postoperative chemotherapy, but should just continue endocrine therapy. Those with significant residual disease at time of surgery with a high PEPI score are high risk and would be given postoperative chemotherapy. PEPI is used to guide postoperative therapy in a number of neoadjuvant breast cancer trials (NCT01723774, NCT02236572, NCT01923168, NCT01953588).
Subject Population:	• 49-61 participants • Female • Age: 18-100

	• Stage T2 or greater ER+/ Her2- breast cancer
Trial Type:	Interventional
Type of Control:	Randomized
Description of Study Agent(s):	1. FASLODEX® Fulvestrant 500 mg IM given days 1, 15, 28, then every 4 weeks as per standard of care (SOC). 2. With or without Enzalutamide 160 mg daily. If pre- or peri-menopausal, patients will also receive goserelin 3.6 mg sq every 4 weeks (or equivalent) as per standard of care (SOC).
Study Duration:	1. Treatment duration: until disease progression, unacceptable drug-related toxicity or planned surgery. 2. Patient study duration, including follow-up: up to 5 years. 3. Total study duration, including data analysis: approximately 7 years.

SCHEMATIC OF STUDY DESIGN



LIST OF ABBREVIATIONS

ACRONYM	DESCRIPTION
AE	adverse event
AI	aromatase inhibitor
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AR	androgen receptor
ASCO	American Society for Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
BC	breast cancer
CBC	complete blood count
CBR	clinical benefit rate
CFR	Code of Federal Regulations
cGCP	current good clinical practice
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CNS	central nervous system
CRF	case report form
CRPC	castration-resistant prostate cancer
CT	computed tomography
CTC	circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease-free survival
DHT	dihydrotestosterone
DLT	dose-limiting toxicity

DSM	data and safety monitoring
DSMC	Data and Safety Monitoring Committee
eCRF	electronic case report form
ER	estrogen receptor
FDA	Food and Drug Administration
G(1/2)	grade of adverse event
GCP	good clinical practice
IB	investigator's brochure
IHC	immunohistochemistry
IIT	investigator-initiated trial
IM	intramuscular
INR	international normalized ratio
IRB	institutional review board
LOI	letter of intent
MBC	metastatic breast cancer
mg	milligram
MRI	magnetic resonance imaging
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	maximum tolerated dose
NCI	National Cancer Institute
ORR	overall response rate
OS	overall survival
pCR	pathologic complete response
PEPI	preoperative endocrine prognostic index
PFS	progression-free survival
PI	principal investigator
PK	pharmacokinetics
PO	by mouth

PR	progesterone receptor
PS	performance status
PTT	partial thromboplastin time
RCB	residual cancer burden
SAE	serious adverse event
SOC	standard of care
TNBC	triple-negative breast cancer
U/S	ultrasound
UAP	unanticipated problem
UCCC	University of Colorado Cancer Center
ULN	upper limit of normal

TABLE OF CONTENTS

1. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 BACKGROUND AND SIGNIFICANCE

Breast cancer is considered a genetically heterogeneous and biologically diverse disease. We currently subdivide breast cancer by ER and Her2 status, in part because these markers represent important predictive biomarkers that guides treatment with discernible survival benefits. Endocrine therapies that target estrogen receptor (ER) signaling pathways play a critical role in the treatment of patients with ER+ disease, even in the advanced setting (1). The androgen receptor (AR) is expressed in most breast cancer specimens, though its functional role in initiating or driving malignancy is not yet well understood. In a study of 3093 breast cancers, AR expression (10% or more nuclear staining by immunohistochemistry [IHC]) was observed in 77% of invasive breast tumors and across all molecular phenotypes, but is expressed in up to 91% of ER+ BC (1-3).

In ER+ BC, AR expression is associated with resistance to anti-estrogen therapy. Tamoxifen-resistant breast tumors have a high ratio of AR-to-ER expression, while tumors that respond to tamoxifen express approximately equal amounts of AR and ER, as does adjacent uninvolved epithelium (4). Furthermore, a high ratio of percent cells positive for nuclear AR versus ER, a ratio of AR:ER ≥2.0 indicated an over four fold increased risk for failure while on tamoxifen (HR = 4.43) and had an independent effect on risk for failure above ER % staining alone. AR:ER ratio is also an independent predictor of disease-free survival (HR = 4.04, 95% CI: 1.68, 9.69; p = 0.002). One explanation for this is that AR signaling, which overlaps considerably with ER signaling, may take over from ER if ER signaling is blocked (5). This would lead to tumor cell survival and proliferation. In addition, the mechanism of action of an aromatase inhibitor is to block the conversion of androstenedione to estrogen, thereby increasing the concentrations of androgens that could, in turn, potentially stimulate the AR on tumor cells to enhance growth (6).

The anti-AR therapy enzalutamide blocks not only dihydrotestosterone (DHT)-mediated growth of BC cells, but also estradiol-mediated growth. In addition, in preclinical models of ER+/AR+ breast cancer enzalutamide is just as effective as tamoxifen in blocking estradiol-mediated growth *in vivo* (4). These findings suggest that AR influences breast tumor biology and is an independent predictor of response to anti-estrogen therapies, but perhaps even more importantly, that those patients who relapse on anti-ER therapies may benefit from anti-AR therapies, either up-front in combination with ER-targeted therapies, or following disease progression. New evidence is arising that nuclear-translocated AR serves as an important co-factor regulating DNA binding of activated ER, and that AR signaling may become important for tumor cell survival in the absence of estradiol (5).

In summary, although effective hormonal therapies are available for the treatment of ER+/PgR+ advanced breast cancer, advanced disease remains incurable and currently approved treatments have significant side effects. Taken together, nonclinical and clinical data suggest a potential role of AR signaling in the development of resistance to hormonal treatment. Improvements in the identification of biomarkers that predict benefit from a given therapy are needed to ensure that patients receive the agents from which they are most likely to benefit and to minimize their exposure to toxic agents unlikely to provide benefit. The phase 2 study described herein is designed to address these needs.

1.2 SUMMARY OF RELEVANT CLINICAL EXPERIENCE WITH ENZALUTAMIDE

Medivation and Astellas Pharma, Inc. are co-developing enzalutamide for the treatment of cancer. Enzalutamide is an AR inhibitor that acts on different steps in the AR signaling pathway. Enzalutamide has been shown to competitively inhibit androgen binding to ARs and inhibit AR nuclear translocation and interaction with DNA. The United States (US) Food and Drug Administration (FDA) approved Xtandi (enzalutamide) capsules in August 2012 based on a benefit in overall survival for men with metastatic castration-resistant prostate cancer (CRPC) who previously received docetaxel therapy (14). In men with prostate cancer, the maximum tolerated dose (MTD) was determined to be 240 mg daily, but after review of the safety and efficacy data available, the optimal dose of enzalutamide was determined to be 160 mg/day. More than 4200 subjects and patients have been enrolled worldwide in complete and ongoing clinical trials evaluating enzalutamide as of October 2012.

The most common adverse reactions (drug-related) (≥ 5%) in patients treated with enzalutamide (N = 800) in the phase 3 study CRPC2 (AFFIRM) (N = 1199) were asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension (12). Discontinuations due to adverse events were reported for 16% of enzalutamide-treated patients and 18% of placebo-treated patients. The most common adverse event leading to treatment discontinuation was fatigue (0.6% of enzalutamide-treated patients and 0.3% of placebo-treated patients). The most common adverse reaction leading to treatment discontinuation was seizure, an identified risk and a targeted medical event, which occurred in 0.9% of the enzalutamide-treated patients and none (0%) of the placebo-treated patients.

The use of enzalutamide in women with breast cancer is under investigation. In the completed study, MDV3100-08 (NCT01597193), 160 mg/day was determined to be the recommended phase 2 dose. The PK and safety profile in women was found to be similar to that observed in men. The dose-expansion portion of this study found evidence of some activity of enzalutamide at 160 mg/day as a single agent in women with AR+ breast cancer in all subtypes of breast cancer. Enzalutamide was combined with either anastrozole or exemestane in women with ER+ breast cancer. Enzalutamide was found to be a potent CYP3A4 inducer and reduced the AUC of anastrozole by 80% and reduced the AUC of exemestane by about 50%. Double dose exemestane, i.e., 50 mg/day was found to be safe in combination and provided full suppression of estradiol. This dosing was then used for a randomized double blind phase II trial of exemestane +/- enzalutamide in ER+ AR+ MBC Protocol MDV3100-12. This trial has been completed, but is currently maturing for efficacy endpoints. No new safety signals were found. In addition, the use of enzalutamide in women with advanced AR+ TNBC was evaluated in a single-arm, open-label phase 2 study, MDV3100-11 (NCT01889238). Results have been reported at ASCO 2015. A trial of enzalutamide plus trastuzumab is ongoing in Her2+ AR+ BC. (See preliminary studies).

As part of the phase I study, enzalutamide was combined with full dose fulvestrant. Preclinical modeling showed synergistic inhibitory effects on tumor cell growth (13). Fulvestrant is not significantly metabolized by CYP3A4. In this substudy, 11 patients with ER+ AR+ BC had loading doses of fulvestrant 500 mg every 2 weeks for one month, then were treated with fulvestrant 500 mg IM every 4 weeks as standard of care (13). Open label enzalutamide at 160 mg po daily was added. PK was done for both drugs to look for interactions. The median age of these patients was 59 (53-78) years, and 64% had

prior treatment for metastatic disease. No significant PK interaction was found and no new safety signals were found. Several patients remained on this combination treatment for over a year.

1.3 PRINCIPLES OF NEOADJUVANT THERAPY FOR BREAST CANCER

Randomized trials demonstrate similar long-term outcomes when patients are given the same treatment preoperatively compared with postoperatively. Neoadjuvant therapy can render surgically inoperable patients operable and offers potential benefits in patients with operable breast cancer. Importantly, neoadjuvant systemic therapy can improve rates of breast conservation therapy eligibility and provides an opportunity to observe clinical and pathologic response to systemic therapy in an individual patient.

Although most preoperative therapy is in the form of chemotherapy, there is a growing interest in treating ER+ breast cancer with preoperative endocrine therapy (15, 19). The rationale is that in general:

- Endocrine therapy has a greater impact on disease-free survival compared with chemotherapy in the adjuvant setting
- The utility of chemotherapy for patients with luminal breast cancer (especially luminal A breast cancer) or for those tumors with low OncotypeDx recurrence scores or low risk Mammaprint scores may be negligible
- Can facilitate breast conservation
- Can render inoperable patients operable
- Provides important prognostic information at an individual patient level based on response to therapy
- Allows time for genetic testing
- Allows time to plan breast reconstruction in patients electing mastectomy
- May allow sentinel lymph node biopsy alone if a positive axilla is cleared with therapy
- May provide an opportunity to modify systemic treatment if no preoperative therapy response or progression of disease

1.4 PREOPERATIVE ENDOCRINE THERAPY

Trials comparing neoadjuvant endocrine therapy to neoadjuvant chemotherapy in ER+ BC show similar response rates, ranging from 48 to 89% (endocrine) and 64–85% (chemotherapy) (16). Semiglazov and colleagues compared four cycles of neoadjuvant chemotherapy to three months of endocrine therapy in 239 patients. Objective response rates were similar (63.6% vs. 64.5%; $p > 0.5$), but with more lumpectomies performed for patients on endocrine therapy (33% vs. 24%; $p = 0.058$) (17). Pathologic complete response (pCR) is less commonly achieved in luminal breast cancers regardless of the type of neoadjuvant systemic therapy given (18).

Main postmenopausal neoadjuvant endocrine trials (15).							
Study	Patient population	N	Median age	Treatment	Duration	Clinical response	Biomarker response
P024Eiermann et al. [9]; Ellis et al. [26]	HR+ve BC; at study entry ineligible for BCS.	337	67	Letrozole vs. Tamoxifen	4 months	ORRa letrozole 55% vs. tamoxifen 36%; (P < 0.001); BCS favouring letrozole (45% vs. 35%; p = 0.022).	Greater Ki67 reduction at 16 weeks in letrozole arm (p = 0.0009).
IMPACTSmith et al. [10]; Dowsett et al. [28]	ER+ve BC; at study entry operable or locally advanced potentially operable.	330	73	Anastrozole vs. Tamoxifen vs. Combination	3 months	ORRa,b no significant differences; BCS favoured anastrozole arm (44% vs. 31%; p = 0.23).	Greater Ki67 reduction at 2 and 12 weeks in anastrozole arm (p = 0.004, p = 0.001); Higher 2 week Ki67 associated with lower RFS (p = 0.004).
PROACTCataliotti et al. [13]	HR+ve BC; at study entry large, operable, or potentially operable BC.	451	67	Anastrozole vs. Tamoxifen (neoadjuvant chemotherapy allowed)	12 weeks	All patients ORRa,b no significant differences (p = 0.38, p = 0.54).For ET only patients (n = 314) ORRa favoured anastrozole (33% vs. 27%, p = 0.04); improvement in surgical feasibility favouring anastrozole (43% vs. 31%, p = 0.04).	
Z1031Ellis et al. [8]	Clinical stage T2-T4c, ER+ve BC; at study entry marginal for BCS, only eligible for mastectomy or inoperable.	377	65	Exemestane vs. Letrozole vs. Anastrozole	16–18 weeks	cRRb exemestane 63% vs. letrozole 75% vs. anastrozole 69%.	No significant difference in Ki67 reduction at 16–18 weeks (p = 0.45); no difference in achieving PEPI 0 between arms (anastrozole 17% vs. letrozole 15.9% vs. exemestane 15.6%; p = 0.9).

Ki67 suppression after 2, 4, 12, or 16 weeks of endocrine therapy is greater with anastrozole vs. tamoxifen (20) or with letrozole vs. tamoxifen (21). The preoperative endocrine prognostic index (PEPI) was developed from the P024 trial and validated in the IMPACT trial (22). PEPI is a model that combines ER, pathologic tumor site, nodal status, and Ki67 score at time of surgery to predict subsequent risk of recurrence. Those patients with a low PEPI score of 0 are unlikely to benefit from postoperative chemotherapy, but should just continue endocrine therapy. Those with significant residual disease at time of surgery with a high PEPI score are high risk and would be given postoperative chemotherapy. PEPI is used to guide postoperative therapy in a number of neoadjuvant breast cancer trials (NCT01723774, NCT02236572, NCT01923168, NCT01953588).

Fulvestrant is chosen as the standard of care and the agent to combine with enzalutamide in part because fulvestrant has been shown to be more active against ER+ BC than AIs in the FIRST trial, and it appears not to have adverse PK interactions with enzalutamide as described in the preliminary studies section below. The FIRST trial randomized women with metastatic ER+ BC in first line endocrine therapy to fulvestrant at the 500 mg dosing or to anastrozole 1 mg po daily. The clinical benefit rate (CBR), progression-free survival (PFS), and overall survival (OS) were 72.5% vs 67%, 23.4 months vs 13.1 months, and 54.1 months vs 48.4 months, respectively (23, 24). These findings are undergoing phase III confirmation in the FALCON trials (NCT01602380). The ALTERNATE trial, currently accruing in the cooperative groups, randomized women with cT2-4 N0-3 M0 ER+/Her- breast cancer to anastrozole, fulvestrant, or the combination for 6 months prior to surgery (NCT01953588).

1.5 PRELIMINARY STUDIES/ PROGRESS REPORT

Drs. Richer and Elias received a Department of Defense Clinical Translation Research Award to study the role of AR signaling and the effect of inhibiting that signal in breast cancer in both the preclinical and clinical setting. Given a long-standing relationship with Medivation, both Medivation and Astellas agreed to collaborate in these efforts. The current LOI addresses the need to obtain serial biopsies from patients receiving enzalutamide for breast cancer. We plan to do these clinical trials at multiple selected sites.

Preclinical modeling demonstrated that enzalutamide blocked the ability of AR to translocate to the nucleus with or without ligand (4-OH testosterone) and that this caused significant cytotoxicity both in vitro and in vivo in a variety of breast cancer cell lines and patient-derived xenografts (7). Despite the fact that enzalutamide does not bind ER, it blocked ER signaling and estradiol growth stimulation in ER+BC cells. Further laboratory investigation has now shown that AR binds directly with ER and regulates the DNA binding sites for ER (8).

Thus far, trials sponsored by Medivation and/or Astellas have established:

- Phase I evaluation of single agent enzalutamide (9, 10): PK of enzalutamide not different in women; RP2D 160 mg po daily. Toxicities similar to that of men – largely G1/2 fatigue, nausea, hot flashes, and occasional mild transaminitis. Because of concern over possible seizure risk (men with prostate cancer ~6/3000 had seizures, but most of these had had brain metastases or CNS surgery), women with brain metastases have been excluded from all enzalutamide trials.
- Phase I/PK studies (11-13): enzalutamide with anastrozole, single dose exemestane, double dose exemestane, and fulvestrant – AUC of anastrozole reduced by ~80%; AUC of exemestane reduced by ~50%; AUC of double dose exemestane with concurrent enzalutamide was equivalent to single dose exemestane when given alone; and the AUC of fulvestrant was not obviously affected by enzalutamide. Anti-tumor efficacy is documented in each of these trials.
- Phase II enzalutamide in AR+ TNBC (12): 29% clinical benefit rate at 24 weeks.
- Phase II randomized trial of double dose exemestane +/- enzalutamide in AR+ ER+ BC: results maturing.
- The phase I of fulvestrant/enzalutamide combination established safety and lack of PK interaction, but only included 11 patients (13). Preclinical modeling of this combination showed synergy (13).

This is a randomized two arm phase II study to further evaluate the efficacy of fulvestrant plus enzalutamide compared to single agent fulvestrant in postmenopausal women with locally advanced AR+/ER+/Her2- BC who will have local surgery after ~4 months on treatment. After consent, the patients have a tissue biopsy. Half the patients will get fulvestrant alone (standard dosing) and half the patients will get fulvestrant plus enzalutamide. At ~4 weeks, a biopsy will be done and therapy will be continued. Hormone therapy will continue for ~4 months at which point the patients will undergo surgical resection. %PEPI score=0 evaluated at surgery will be used as the primary efficacy endpoint using the Ellis methodology [4, 5]. Prior trials have demonstrated a 16% rate of PEPI scores of 0 with preoperative antiestrogens for 4 months. Fulvestrant is at least as active as aromatase inhibitors [6], and lacks PK interaction. The FIRST trial, at the now standard dose of 500 mg, established that fulvestrant was at

least as active as aromatase inhibitors in women with metastatic ER+ BC, demonstrating superior PFS and OS for fulvestrant (23, 24).

2. HYPOTHESES AND OBJECTIVES

2.1 SPECIFIC AIMS

This randomized phase 2 study is designed to evaluate whether the addition of enzalutamide to fulvestrant treatment for ~4 months in women with locally more advanced breast cancer that is ER positive and Her2 normal will improve the PEPI score at time of surgery.

2.2 RATIONALE

AR expression is associated with resistance to anti-estrogen therapy. Its blockade may enhance response.

2.3 CLINICAL HYPOTHESIS

The addition of enzalutamide to patients receiving fulvestrant will improve the PEPI score at time of surgery.

2.4 LABORATORY HYPOTHESES FROM SERIAL BIOPSIES

1. In the luminal (ER+/AR+) tumors, decrease in Ki67 after ~4 weeks of treatment to below 10% is associated with response to therapy and will correlate with progression-free survival (PFS).
2. Pretreatment molecular characteristics (such as AR:ER ratio in ER+ tumors, Her2 status, PI3K pathway mutations, or others based on further profiling of sensitive versus resistant cell line and patient samples) will be associated with lesser response and poorer PEPI score. AR expression is associated with resistance to anti-estrogen therapy. Its blockade may enhance response.

2.5 OUTCOME MEASURES

2.5.1 PRIMARY OBJECTIVE

Evaluate the rate of PEPI score equal to 0 at 16 weeks post treatment for each of the two treatment arms separately.

2.5.2 SECONDARY OBJECTIVES

1. To determine the percentage of progression-free survival (PFS), clinical response rate (by physical exam and breast imaging) after 16 weeks of therapy for the single drug arm and combination of enzalutamide/fulvestrant arm separately.
2. To assess the association between PEPI score and the clinical outcomes such as PFS and clinical response for all the subjects.
3. To confirm the safety profile of the combination.
4. To determine the extent of AR expression and signaling in breast tissue, to evaluate the effect of the drug (s) on the tumor, and to evaluate the relationship of these effects on clinical outcomes for the two arms separately.

3. STUDY DESIGN AND RESEARCH METHODS

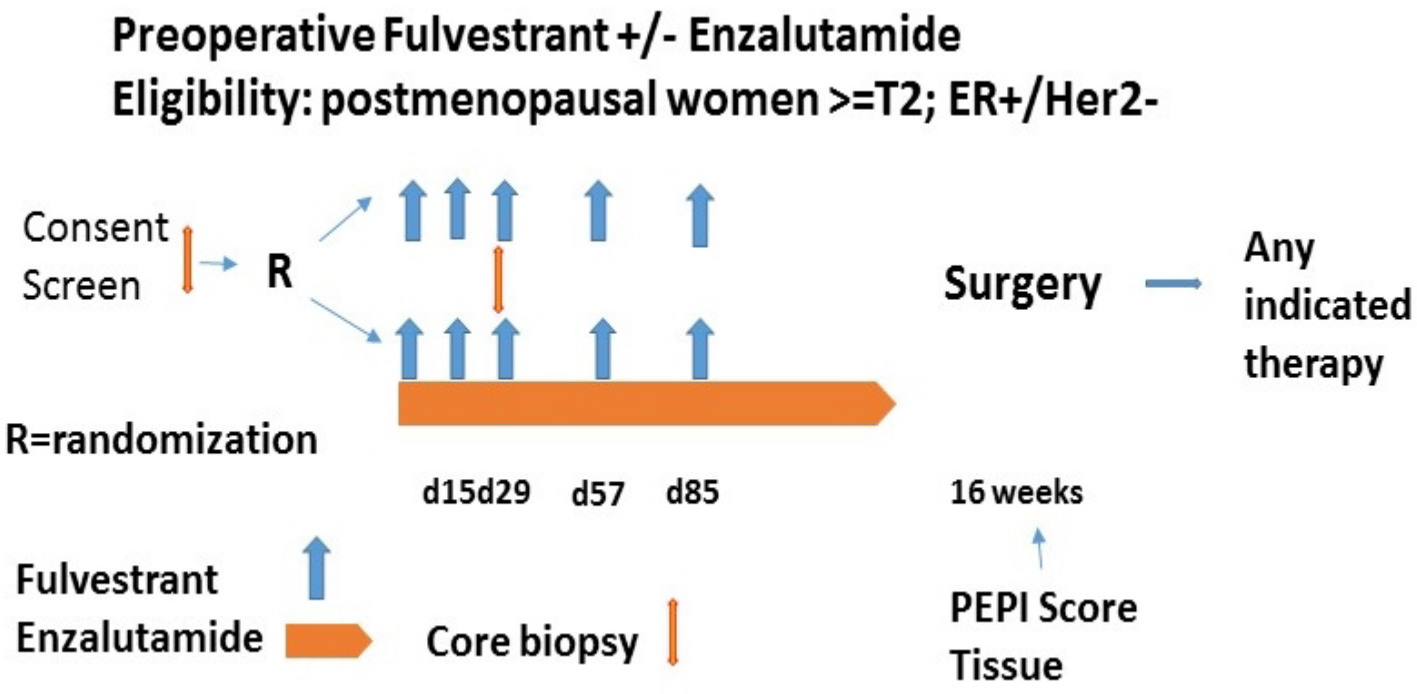
3.1 STUDY DESIGN

Randomized, open-label treatment consisting of:

- Fulvestrant 500 mg IM given days 1, 15, 28, then every 4 weeks as per standard of care (SOC).
- With or without Enzalutamide 160 mg daily.

If pre- or perimenopausal, patients will also receive goserelin 3.6 mg sq every 4 weeks (or equivalent) as per standard of care (SOC).

3.2 STUDY SCHEMA



3.3 STUDY PERIODS

The study periods will be as follows for all patients:

- Screening: Up to 28 days before treatment;
- Treatment: Day 1 of treatment through completion of surgery;
- Safety follow-up: 30 days after surgery;
- Follow-up period: until disease progression or 5 years, whichever comes first.

3.4 SAMPLE SIZE

49 to 61 patients will be randomized and treated. Serial tumor biopsies will be obtained – pre-enzalutamide treatment and at ~4 weeks on therapy. Tumor will be collected at time of surgery as well.

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1 INCLUSION CRITERIA

1. ER+ Her2- breast cancer
2. Stage at least T2 or greater
3. Planned to get local surgery
4. Postmenopausal, or if pre- or peri- menopausal, then will need to have concurrent ovarian suppression. Pre- or peri- menopausal subjects must have a negative urine pregnancy test confirmed at screening.
5. Female, at least 18 years of age
6. ECOG PS 0-2
7. Able to swallow study drug and comply with study requirements
8. ANC $\geq$1000/uL, platelets $\geq$75,000/uL at screening visit
9. Total bilirubin $\leq$ 1.5 times upper limit of normal (ULN) at the screening visit unless an alternate nonmalignant etiology exists (eg, Gilbert's disease)
10. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\leq$ 3 times ULN or $\leq$ 5 times ULN if patient has documented liver metastases
11. Creatinine $\leq$ 1.5 times ULN
12. INR < 1.5 times ULN, or if on warfarin, can safely transition off for biopsy
13. Willing to donate blood for research at 4 time points
14. Willing to undergo core biopsies for research at study entry and at ~4 weeks
15. Willing to donate tissue to research from the surgical specimen
16. Written informed consent obtained prior to biopsies and blood samples
17. Agreement to exercise appropriate use of contraception. Subjects should use 2 acceptable methods of birth control (one of which must include a condom as a barrier method of contraception) starting at the time of screening for an enzalutamide study and continuing throughout the course of treatment and for at least three months after enzalutamide is discontinued.

4.2 EXCLUSION CRITERIA

1. Current or previously treated brain or leptomeningeal metastases
2. History of seizures
3. Prior treatment with an anti-androgen (abiraterone, ARN-509, bicalutamide, enzalutamide, ODM-201, TAK-448, TAK-683, TAK-700, VT-464)
4. Systemic estrogens or androgens within 14 days before initiating therapy. Vaginal estrogens are allowed if necessary for patient comfort.
5. Not on full dose anticoagulants

4.3 WITHDRAWAL

Participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

An investigator may also terminate a participant's enrollment in the study if any clinical adverse event (AE), laboratory abnormality, non-compliance, lost to follow-up, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.

5. STUDY AGENT

5.1 ENZALUTAMIDE

5.1.1 GENERAL INFORMATION

The study drug, enzalutamide, is approved in the US to treat men with metastatic CRPC who previously received docetaxel.

5.1.2 ENZALUTAMIDE PRODUCT CHARACTERISTICS

Enzalutamide, also known as MDV3100, has the chemical name 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-*N*methylbenzamide. The drug substance is formulated in the surfactant caprylocaproyl polyoxylglycerides, also known as Labrasol. The product will be supplied as white to off-white soft gelatin capsules containing 40 mg of enzalutamide.

5.1.3 ENZALUTAMIDE PACKAGING

Enzalutamide is packaged in bottles with induction-sealed child-resistant caps labeled with the study protocol number, contents, directions for use, storage directions, clinical trial statement, and sponsor name. Each bottle contains 120 capsules (30-day supply).

5.1.4 ENZALUTAMIDE STORAGE

Enzalutamide study drug is to be handled and stored safely and properly in accordance with the study drug label.

5.1.5 DIRECTIONS FOR ADMINISTRATION OF ENZALUTAMIDE

The daily dose of enzalutamide is 160 mg/day in 4 capsules (40 mg each) given by mouth. Patients should self-administer enzalutamide study drug by mouth once daily, with or without food, starting on day 1. The capsules should be swallowed whole without chewing, dissolving, or opening them. Patients will self-administer the study drug at home. Patients should not make up missed or vomited doses; dosing should resume on the next calendar day unless otherwise instructed.

5.1.6 DIRECTIONS FOR DOSE MODIFICATION OF ENZALUTAMIDE

Patients who experience a grade 3 or higher toxicity that is attributed to enzalutamide study drug and cannot be ameliorated by the use of adequate medical intervention may interrupt treatment with enzalutamide. Subsequently, the enzalutamide dosing may be restarted at the original dose (160 mg/day, 4 capsules) or a reduced dose (80 mg/day, 2 capsules). Treatment interruption and reinitiation should be discussed with the principal investigator.

5.1.7 Treatment Compliance

Study drug accountability will be performed to document compliance with the dosing regimen. Patients will be asked to return all bottles of study drug at study visits. Patients who forget to return bottles will be asked to return them at the next study visit.

5.1.8 Drug Inventory and Accountability

Drug inventory and accountability records for the study drugs will be kept by the investigator/pharmacist. Used or unused study drug may be destroyed at the study site according to standard institutional procedures if the sponsor agrees with the procedure, and after drug accountability has been conducted by the sponsor or representative, unless otherwise approved.

5.1.9 Effects of Enzalutamide on Exposure to Other Drugs

Clinical data indicate that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Concomitant use of enzalutamide with drugs with a narrow therapeutic index that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (eg, phenytoin, warfarin), and CYP2C19 (eg, S-mephenytoin) should be avoided if possible as enzalutamide may decrease their exposure. If coadministration with warfarin cannot be avoided, additional INR monitoring should be conducted.

5.1.10 Drugs that May affect Exposure to Enzalutamide

5.1.10.1 *Drugs that Inhibit or Induce CYP2C8*

Coadministration of a strong CYP2C8 inhibitor (eg, gemfibrozil) increased the composite AUC0-∞ of enzalutamide plus its active metabolite in healthy volunteers by 2.2-fold; therefore, coadministration of enzalutamide with strong CYP2C8 inhibitors should be avoided if possible. If coadministration of enzalutamide with strong CYP2C8 inhibitors cannot be avoided, the enzalutamide dose should be reduced to 80 mg once daily. If coadministration of the strong inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor.

The effects of CYP2C8 inducers on the PK of enzalutamide have not been evaluated in vivo. Coadministration of enzalutamide with strong or moderate CYP2C8 inducers (eg, rifampin) may alter the plasma exposure of enzalutamide and should be avoided if possible. Selection of a concomitant medication with no or minimal CYP2C8 induction potential is recommended.

5.1.10.2 *Drugs that Induce CYP3A4*

The effects of CYP3A4 inducers on the PK of enzalutamide have not been evaluated in vivo. Coadministration of enzalutamide with strong CYP3A4 inducers (eg, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) may decrease the plasma exposure of enzalutamide and should be avoided if possible. Selection of a concomitant medication with no or minimal CYP3A4 induction potential is recommended. Moderate CYP3A4 inducers (eg, bosentan, efavirenz, etravirine, modafinil, nafcillin) and St. John's Wort may also reduce the plasma exposure of enzalutamide and should be avoided if possible.

5.1.11 Precautions Regarding Concomitant Medications

Refer to the following websites for updated lists of CYP inhibitors, inducers, and substrates.

- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#potency
- http://medicine.iupui.edu/clinpharm/ddis/table.aspx

5.2 FULVESTRANT

Fulvestrant is an ER antagonist indicated for the treatment of postmenopausal women with hormone receptor-positive advanced breast cancer. Unlike the selective ER modulator tamoxifen, which displays mixed antagonist/agonist properties, fulvestrant has no agonist effects. Fulvestrant binds, blocks, and increases degradation of the ER, leading to an inhibition of estrogen signaling. This distinctive mode of action may overcome tumor resistance to previous endocrine agents. The increased degradation of the ER by fulvestrant may also limit cross-talk between growth factor receptor and ER-mediated signaling pathways and thus increase the duration of response observed with fulvestrant treatment.

Per the USPI8, the recommended dose of fulvestrant is 500 mg administered by IM injection on days 1, 15, and 29 and once monthly thereafter. The most common clinically significant adverse reactions occurring in ≥ 5% of patients receiving fulvestrant 500 mg are injection site pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, pain in extremity, hot flush, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea, and constipation. In addition, ≥ grade 1 elevations in AST, ALT or alkaline phosphatase were observed in > 15% in pooled analysis of fulvestrant trials, with grade 3 to 4 increases observed in 1% to 2% of patients. Clinical data show that fulvestrant does not affect the pharmacokinetics of midazolam (a sensitive CYP3A4 substrate) and rifampin and enzalutamide (a potent CYP3A4 inducer) had no effect on the pharmacokinetics of fulvestrant.

5.3 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

The Investigator must maintain accurate records (including dates and lot numbers) of all study drug supplies received. All study drug supplies issued to, used by, and returned by each patient must be recorded on a Drug Accountability Log completed by the Investigator or designee. All remaining study supplies, opened or unopened, must be returned to the Sponsor (or designee) at the end of the study or destroyed on site according to the site's standard operating procedures only after study drug accountability has been completed and with approval of the Study Monitor. All records must be made available to the Sponsor (or designee) and appropriate regulatory agencies upon request.

6. STUDY PROCEDURES AND SCHEDULE

6.1 STUDY SCHEDULE

Study Phase	Screening	Treatment				Preop	Postop	Follow-up
Study Week	-4 to -1	1 [11]	5	9	13	17	21	Varies [1]
Window (Days)	28	n/a	+/- 7	+/- 7	+/- 7	+/- 14	+/- 28	+/- 7
Informed Consent	X							
Eligibility	X							
Medical History	X							
Archived Tissue Collection [2]	**X**						**X**	
Breast Imaging [7]	X					X		
Staging [3]	X							
ECOG	X							
Height/Weight	X							
Physical Exam	X			X		X	X	
Breast Exam	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	
Study Drug Dispensing [4]		**X**		**X**				
Fulvestrant [10]		X	X	X	X			
Tumor Biopsy		**X [5]**	**X**				**At surgery**	
Hematology & Serum Chemistry [6]	X	X [9]	X	X	X	X	X	
PT/INR, PTT [12]	X							
Urine Pregnancy Test [13]	X							
Circulating Tumor Biomarkers	**X**	**X [9]**	**X**	**X**	**X**	**X**	**X**	
CTCs [8]	**X**					**X**	**X**	
Survival & Recurrence Follow-up								**X**

[1] Follow-up at least every 6 months out to 2 years and then yearly out to 5 years (may be done by telephone).

[2] From primary lesion previously biopsied.

[3] CT with contrast (unless medically contraindicated) of chest, abdomen, and pelvis and bone scan as clinically indicated. MRI is acceptable if CT not possible.

[4] Refill every 8 weeks as long as patient remains on active treatment.

[5] Before treatment, but after eligibility determined.

[6] Hematology: CBC with auto differential. Chemistry: albumin, alkaline phosphatase, ALT (alanine aminotransferase), AST (aspartate transaminase), blood urea nitrogen and creatinine; Ca++, Cl-, K+, Na+; glucose (non-fasting), total bilirubin, total CO2 (bicarbonate), total protein.

[7] Mammogram +/- U/S at baseline (could be obtained within 2 months); MRI optional. Preop imaging must be done if breast conserving surgery is planned. Preop imaging is optional if mastectomy is planned.

[8] CTCs will only be collected at the coordinating center at the start of the study. External sites will be notified when collection should commence at their site. Samples should be collected before treatment, but after eligibility determined. Subsequent samples will only be collected if pretreatment is positive.

[9] Only one sample is needed pretreatment (either during screening or prior to treatment on C1D1).

[10] Administer by IM injection on days 1, 15, and 29 and once monthly thereafter.

[11] If pre- or perimenopausal, patients will also receive goserelin 3.6 mg sq every 4 weeks (or equivalent) as per standard of care (SOC).

[12] Collected at screening and as required per institutional standard.

[13] If woman of child bearing potential only.

Bold represents non-SOC events.

6.2 DRUG DISPENSING

An 8 week supply of enzalutamide (bottles of 120 capsules) will be provided to each patient at a time (provided by Astellas/Medivation) and dispensed by the research pharmacy. Additional bottles may be dispensed to accommodate necessary windows for subsequent visits or for accidental wastage.

6.3 LABORATORY PROCEDURES/ EVALUATIONS

6.3.1 BLOOD

Routine blood tests (chemistries, hematology) will be obtained every month as clinically indicated. Tumor markers to be followed every 1-2 months as clinically indicated.

Blood for potential pharmacogenomics testing will be obtained at baseline. The white cell pellet required for this sample will be obtained from the baseline plasma vacutainer.

Plasma for tumor related exosomes and other circulating tumor products will be obtained each cycle on day 1 (10 ml).

Blood for circulating tumor cells will be obtained before treatment, but after eligibility is determined. Subsequent samples will be obtained at pre-op and post-op only if pretreatment positive.

6.3.1.1 *Baseline*

1 plasma vacutainer (green top, lithium heparin, 10ml)

1 serum vacutainer (red top, 10ml)

1-2 tubes for CTC sample collection (up to 20ml)

6.3.1.2 *Day 1 each cycle*

1 plasma vacutainer (green top, lithium heparin, 10ml)

6.3.1.3 *Preoperatively*

1 plasma vacutainer (green top, lithium heparin, 10ml)

1-2 tubes for CTC sample collection (up to 20 ml)

6.3.1.4 *Postoperatively*

1 plasma vacutainer (green top, lithium heparin, 10ml)

1-2 tubes for CTC sample collection (up to 20ml)

6.3.2 SERIAL BIOPSIES

At baseline and at ~4 weeks into treatment, the patients will have a tumor needle core biopsy obtained (up to 3 cores), divided into a formalin fixed, paraffin embedded specimen and a fresh frozen specimen to be analyzed. Tissue will be used for future studies, if subjects consent to tissues to be banked. See study procedure manual for shipping and other instructions. The purpose of the baseline pre-enzalutamide tumor tissue is to gather an understanding of ER+ breast cancers that may or may not benefit from AR signaling inhibition. The biopsy 4 weeks into treatment is taken at the time that both drugs are at their steady state concentrations (e.g., following the loading doses of

fulvestrant, and at least 4 half-lives of exposure to enzalutamide (T1/2 = 5.7 days). This will examine the subacute effects of this treatment on the tumor tissue, on AR and ER signaling. In addition, tumor will be obtained from the surgical specimen at time of surgery.

7. RISKS AND BENEFITS

7.1 STUDY RISKS

- Clinical toxicities of fulvestrant (standard agent) plus enzalutamide as outlined in package insert and investigator brochure.
- Biopsies (each one is requested of the patient).
- Misuse or inadvertent release of information.
- Identification of the patient by release of comprehensive genomic information.
    - Pharmacogenomic analysis typically does not identify a genetic predisposition to a disease since its analysis typically is restricted to enzymes that metabolize the therapeutically administered agents.
- Low white blood cell count, which may increase risk of infection.
- Blood clot in the lungs (also known as pulmonary embolism).

7.2 POTENTIAL BENEFITS

Summary of knowledge to be gained:

- The % PEPI scores of 0 that can be achieved with fulvestrant plus enzalutamide and with the concurrent control arm of fulvestrant alone.
- Characteristics of breast cancers that benefit or fail to benefit from enzalutamide. A set of putative biomarkers will be identified.
- Mechanisms of resistance to enzalutamide-based treatment that arise in the clinic.

7.3 JUSTIFICATION OF RISKS

The clinical impact of enzalutamide in breast cancer is not yet determined. Because the patients in this study are potentially curable, they will undergo rigorous monitoring with clinical exams every 4 weeks during the preoperative phase. If the tumor appears to progress, the patient can be taken off study and treated accordingly as per the treating physician. Depending on pathology findings and the patient's medical status, postoperative care is at the discretion of the treating physician.

The extent of AR expression that correlates with enzalutamide efficacy is unknown and is an objective of this study; therefore, all patients, including those few that might have "AR-low" breast cancer, will be enrolled to receive standard of care fulvestrant with or without enzalutamide. The choice of this combination was to take advantage of the lack of PK interaction between the two agents and conduct a phase II trial.

7.4 SERIOUS ADVERSE EVENTS

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- Results in death (death solely as a result of disease progression is not a serious adverse event);

- Is life threatening (i.e., the patient was at immediate risk of death at the time of the event). "Life threatening" does not include an event that hypothetically might have caused death if it were more severe. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of the patient's ability to carry out normal life functions);
- Is a congenital anomaly/birth defect;
- Is a medically important event, including seizure.

7.5 SERIOUS ADVERSE EVENT REPORTING

NCI CTCAE 4.03 will be used for adverse event reporting.

Within 24 hours of awareness of a serious adverse event, whether or not related to the study drug, the Investigator or delegated personnel will complete and submit a MedWatch 3500A Form to the sponsor investigator and Astellas, containing all required information (reference 21 CFR 312.32). The sponsor investigator will submit the SAE to any additional regulatory authorities as required. If submission of this SAE to the sponsor investigator or Astellas is not possible within 24 hours, the Investigator's local drug safety contact (IRB, etc.) should be informed by phone.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 30 days following surgery (i.e. completion of the safety follow-up period), after which only recurrence and survival data will be captured. As of 1/5/2023, all patients have completed all protocol-related procedures and therapies, and are well past 30 days post surgery.

Notification of the Principal investigator, Dr. Anthony Elias:

Anthony.elias@ucdenver.edu
Cell 303-638-2018
ACP 5310, MS 8117
1665 North Aurora Court
Aurora, CO 80045

The SAE documentation, including the MedWatch 3500A Form and available source records should be emailed or faxed to:

Astellas Pharma Global Development – United States
Email: Safety-us@us.astellas.com
Fax number: (847) 317-1241

The following minimum information is required:

- Study number/IIT regulatory identifier

- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug

Follow-up information for the event should be sent promptly (within 7 days) as necessary.

The Principal Investigator, Dr. Anthony Elias, will ensure prompt reporting of the SAE to all investigators and co-PIs of the study.

7.6 ADVERSE EVENTS

- An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with study drug.
- An adverse event observed after starting administration of the study drug or comparator drug is called a "treatment-emergent adverse event." Treatment-emergent adverse events will be analyzed and discussed in the clinical study report for this study.

7.7 PROCEDURE IN CASE OF PREGNANCY

- The effect of enzalutamide in pregnant and lactating women is not known, and the exposure of a fetus or nursing infant is considered a potential risk. Enzalutamide can cause fetal harm when administered to a pregnant woman based on its mechanism of action. Subjects receiving enzalutamide are advised to use 2 acceptable methods of birth control (one of which must include a condom as a barrier method of contraception) starting at the time of screening for an enzalutamide study and continuing throughout the course of treatment and for at least three months after enzalutamide is discontinued.
- The Investigator should report the outcome of the pregnancy (independent of outcome, e.g. full term delivery, pre-term delivery, spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly [including anomaly in a miscarried fetus, etc.] in accordance with the same reporting procedure as for SAEs. The date of outcome of the pregnancy, gestational age, date of birth and neonatal data etc., should be included in this information.

7.8 IN CASE OF INJURY

In the event of a side effect or injury, appropriate medical care as determined by the Investigator or his/her designated alternate will be provided. No other compensation of any type will be provided by the study Sponsor.

7.9 SAFETY MONITORING AND REPORTING

As of 1/5/2023, all patients have completed all protocol-related procedures and therapies and are well past 30 days post-surgery. Patients are being followed for relapse and survival only.

8. STUDY OVERSIGHT

8.1 DATA SAFETY AND MONITORING OVERSIGHT

As of 1/5/2023, all patients have completed all protocol-related procedures and therapies and are well past 30 days post-surgery. The DSMC plans to close active monitoring as of its meeting in 4/2023.

8.2 CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with GCP, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by CU Cancer Center Clinical Monitor in accordance with the clinical monitoring plan (CMP), incorporated herein by reference. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of the monitoring reports. As necessary, requests for data clarification or correction will be sent to the appropriate site PI.

8.3 AUDITING

Independent audits will be conducted by the CU Cancer Center DSMC. Independent auditors from the sponsor investigator's authorized representative will be allowed by the site's PI. In addition, audits may be conducted at any time by appropriate regulatory authorities and/or the IRB. During the course of the study and after it has been completed it is likely that 1 or more study site visits will be undertaken by authorized representatives of the Sponsor.

The purpose of the audit is to ensure that the study is being, or has been, conducted and monitored in compliance with the protocol as well as recognized cGCP guidelines and regulations, to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP, as defined herein. These audits will also increase the likelihood that the study data and all other study documentation can withstand a subsequent regulatory authority inspection.

If such audits are to occur, they will be arranged for a reasonable and agreed time.

All reports and patient samples will be identified only by the patient's ID number and the patient's initials in order to maintain patient confidentiality. Additional patient confidentiality issues are covered in the Clinical Trial Agreement and in the informed consent form signed by the patient.

9. STATISTICAL CONSIDERATIONS

9.1 CLINICAL DATA

Age, ethnicity, race, gender, breast cancer histology (ductal, lobular, other), breast cancer subtype (ER, PR, Her2, Ki67, AR), detailed prior treatment history, selected comorbidities (especially insulin,

metformin use), clinical response, type of surgery, surgical pathology, DFS and OS. Details of treatment, including AE, SAE, and compliance.

9.2 RESEARCH LABORATORY DATA WILL INCLUDE

AR IHC quantitation, AR pathway activation, AR localization (nuclear/cytoplasmic), Ki67 and response, cleaved caspase 3, AR mRNA, AR mutational status, AR splice variants, ER IHC quantitation, ER mRNA, RNAseq, whole exome sequencing, proteomic analysis.

9.3 RESEARCH METHOD CONSIDERATIONS

9.3.1 GENERAL CONSIDERATIONS

9.3.1.1 *Analysis populations*

Patients who received at least 4 weeks of treatment will be included in the efficacy analyses. Patients who received at least one dose of enzalutamide will be included for the safety evaluation. We do not anticipate any withdrawal during the first four weeks of treatment. After four weeks, if patients withdraw, they will not be replaced. However, they will be included for the efficacy evaluation.

9.3.1.2 *Randomization*

A total of 51 patients will be randomized into the two arms with 34 patients for the combination arm and 27 for the Fulvestrant arm. If the combination arm stops earlier due to futility, the remaining 12 patients (for stage 2) will move on to other studies.

9.3.2 ANALYSIS METHODS

Summary statistics will be used for the primary outcome the rate of PEPI=0 and the secondary outcomes including the response rate, clinical benefit rate as well as percentage of PFS by 16 weeks. Clinical benefit rate is defined as the proportion of subjects with complete response or partial response or stable disease. Response rate is defined as the proportion of subjects with complete response or partial response. 95% exact confidence intervals will be provided. Kaplan-Meier product limit progression free survival plots will be generated and median progression free time and associated 95% CI will be estimated, the PFS percentage at 16 weeks will be calculated. Descriptive statistics will be used to summarize the safety data such as the DLT for both hematologic and non-hematologic toxicity per type and grade, as well as all collected AE data, which will be listed per patient, and cycle. Spearman correlation coefficient or relative risk will be calculated for the association between PEPI score and the clinical outcomes.

For the biopsy samples, exploratory analyses such as multivariable logistic regression, linear regressions and survival analyses will be required to attempt to classify protein, gene, or TUNEL markers associated with clinical outcomes such as response, clinical benefit and PFS as predictive (of therapeutic impact) or prognostic (of intrinsic tumor biology). Bio-informatics tools such as unsupervised pathway analysis will also be explored.

The following molecular characteristics at baseline will be explored among others:

1. Nuclear to cytoplasmic localization of AR staining.

2. Strength of AR signaling as measured by the expression of downstream AR-regulated genes, which should reflect dependence of the tumor cell on AR function.

3. AR:ER ratio with resistance to anti-estrogen therapy.

9.3.3 Sample Size and Power Consideration

The design is to evaluate the rate of % PEPI = 0 in each of the two arms separately. Since this is a randomized phase II, the two arms are not to be compared directly. A total of 49-61 evaluable patients are required to complete the study.

9.3.3.1 *Combination arm*

We have the expectation that a standard preoperative AI for 4 months would produce PEPI score of 0 in ~16%. We hope to see a rate of 32% for the combination arm. We plan a Simon 2-stage design with 22 patients entered in the first stage (25). If 3 or fewer obtain PEPI score of 0, the trial will terminate. If the trial proceeds to the second stage, a total of 34 patients will be studied. If 8 or fewer patients obtain PEPI score of 0, the drug is rejected. Otherwise the drug combination warrants further evaluation. The minimax two-stage design to test the null hypothesis that P<=0.16 versus the alternative that P>=0.32 has an expected sample size of 27 and a probability of early termination of 0.52. This design has 80% power with the type I error rate of 0.08.

Two-Stage Clinical Trials Sample Size for P0=0.160, P1=0.320, Alpha=0.100, Beta=0.200

N1	R1	PET	N	R	Ave N	Alpha	Beta	Constraints Satisfied
22	3	0.523	34	8	27.73	0.080	0.198	Minimax

9.3.3.2 *Single drug arm*

27 subjects will be randomized into the single drug fulvestrant arm. Exact 90% confidence intervals are summarized in the table below assume the actual rate of PEPI=0 is 15% or higher.

Confidence Intervals for the rate of PEPI=0 based on Clopper-Pearson Exact test for 27 subjects.

Proportion PEPI=0	Lower 90% Limit	Upper 90% Limit
0.15	0.053	0.31
0.16	0.06	0.322
0.17	0.066	0.333
0.18	0.072	0.345

Summary of the results: if the percentage of PEPI=0 is 15% or higher, with 27 subjects, the

lowest 90% confidence

Interval will be higher than 5%. Thus if the true rate of PEPI=0 is 15% or higher, with 27 subjects, the observable rate should be greater than 5%.

9.4 POTENTIAL SCIENTIFIC PROBLEMS

9.4.1 ENZALUTAMIDE MAY NOT HAVE SUFFICIENT ANTI-BREAST CANCER ACTIVITY IN THE CLINIC.

Subsequent studies would then focus on defining the tumor characteristics that most likely would be sensitive to this or other AR signaling inhibitors and identifying rational combinations with enzalutamide to overcome this intrinsic resistance.

9.4.2 INADEQUATE COLLECTION OF TISSUES AND INADEQUATE SERIAL SAMPLES.

We anticipate inadequate specimens in up to 10% of individuals. Each investigator is determined to collect these samples and is experienced in obtaining such specimens. Handling of these tissues is routine in all institutions. All participating sites are experienced NCI designated cancer centers, and have well developed phase I and breast cancer multidisciplinary programs. All sites see a large number of new breast cancer patients per year and have high clinical trial accruals. All of the sites lead investigators are accomplished medical oncologists with experience with phase I/II and III trials. Dr. Elias in collaboration with Dr. Richer, conducted the preoperative hormone trial that established the potential importance of AR and enzalutamide in ER+ breast cancer. University of Colorado has well-established core facilities to perform Nextgen sequencing, tissue banking and processing, and CLIA certified IHC.

9.4.3 INADEQUATE TISSUE BIOPSY SAMPLES IN MORE THAN 10% OF INDIVIDUALS.

We would then consider increasing the patient enrollment to obtain 20 matched serial samples (pre-enzalutamide and after 4 weeks).

9.5 DATA ANALYSIS PLAN

9.5.1 TOXICITY

The study populations will include the following:

- The Safety Population, which will include all patients who received at least 1 dose of enzalutamide;
- The Response Population, which will include all patients who began treatment and did not withdraw from study for reasons other than tumor progression.

Descriptive statistics will be used to summarize the AEs and SAEs for both hematologic and non-hematologic toxicity per type and grade. Safety follow-up: approximately 30 days after the planned surgery.

9.5.2 CLINICAL AND PATHOLOGIC RESPONSE & DFS AND OS

Overall response, target lesion response, non-target lesion response, and PFS analyses will be performed:

- Clinical Response: best response by time of surgery by physical exam and/or breast imaging.

- Pathologic response: PEPI score, RCB score, size of tumor, nodal status, RCB score, Ki67.
- Disease Free Survival: For all patients enrolled, DFS will be defined as the time from the first day of enzalutamide treatment (Study Day 1) until documented disease progression or death, whichever occurs first. For patients who do not die or experience disease progression on study, DFS will be right censored at the day of the last information available for progression assessment. Kaplan-Meier methods will be used to describe DFS by dose level and overall.

Overall Survival: For all patients enrolled, OS will be defined as the time from the first day of enzalutamide treatment (Study Day 1) until documented death from any cause. For patients who do not die or experience death, OS will be right censored at the day of the last information available for survival assessment. Kaplan-Meier methods will be used to describe OS by treatment and PEPI scores.

9.5.3 Receptor Expression

The degree of ER, PR, and AR expression in the nucleus will be reported by IHC strength of staining (0-3+) and % nuclei stained. The relationship between tumor response and degree of AR expression, and/or AR signaling, will be examined. Additional assays for AR signaling, (e.g., gene expression array analyses, mutation analyses, or other immunohistochemistry evaluations) may be performed on remaining tissue to evaluate for molecular phenotypes and patterns associated with activated AR signaling.

10. SOURCE DOCUMENTATION AND RETENTION OF RECORDS

10.1 DATA AND CRFS

The clinical data will be collected on eCRFs and stored in a secure, encrypted REDCap file.

10.2 DATA ACCESSIBILITY AND RECORD KEEPING

The Investigator must make study data accessible to the Study Monitor or other authorized representatives of the Sponsor (or designee) and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each patient must be maintained that includes the signed informed consent form and copies of all source documentation related to that patient. The Investigator must ensure the reliability and availability of source documents from which the information on the case report form was derived.

Investigators must maintain all study documentation for a period of 2 years following the approval date of the drug in breast cancer, or until 2 years after the investigational drug program is discontinued. Study documentation includes the Investigator's Brochure, signed protocol and amendments; signed informed consents; notifications of serious adverse events and related reports; any dispensing and accountability logs; shipping records of investigational product and trial related materials; documentation of the financial aspects of the trial, insurance statement, and signed agreement between involved parties; dated and documented IRB approval, and approval of regulatory authority(ies); normal laboratory values; decoding procedures for blinded trials; initiation visit report; curricula vitae; and all

correspondence pertaining to the conduct of the study. The Sponsor will notify the Study Investigator when any records may be discarded.

11. ETHICS

The PI will ensure that this study is conducted in full conformity with regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56. ICH E6 may also be followed to the extent it has been adopted by and is in accordance with FDA regulations.

12. CONFLICT OF INTEREST

Independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed.by the University of Colorado Denver's (UCD) Office of Regulatory Compliance Conflict of Interest and Commitment Management (COIC) program. Persons with a perceived conflict of interest will have such conflicts managed in a way that is appropriate to their participation in the trial. Conflict of Interest management plans are project-specific and are reviewed at least annually. UCD has integrated the institutional conflict of interest management program with its existing program.

13. REFERENCES

1. Collins LC, Cole KS, Marotti JD, Hu R, Schnitt SJ, Tamimi RM. Androgen receptor expression in breast cancer in relation to molecular phenotype: results from the Nurses' Health Study. Mod Pathol. 2011;24:924-31.
2. Elebro K, Borgquist S, Simonsson M, Markkula A, Jirstrom K, Ingvar C, et al. Combined Androgen and Estrogen Receptor Status in Breast Cancer: Treatment Prediction and Prognosis in a Population-Based Prospective Cohort. Clin Cancer Res. 2015;21:3640-50.
3. Hu R, Dawood S, Holmes MD, Collins LC, Schnitt SJ, Cole K, et al. Androgen receptor expression and breast cancer survival in postmenopausal women. Clin Cancer Res. 2011;17:1867-74.
4. Cochrane DR, Bernales S, Jacobsen BM, Cittelly DM, Howe EN, D'Amato NC, et al. Role of the androgen receptor in breast cancer and preclinical analysis of enzalutamide. Breast Cancer Res. 2014; 16: R7. PMID: 24451109 Designated as Highly Cited by the journal Breast Cancer Research.
5. D'Amato NC, Jacobsen BM, Gordon MA, et al. Androgen receptor supports ER alpha activity and genomic binding in breast cancer. Submitted 2016.

6. Takagi K, Miki Y, Nagasaki S, Hirakawa H, Onodera Y, Akahira J. et al. Increased intratumoral androgens in human breast carcinoma following aromatase inhibitor exemestane treatment. Endocr Relat Cancer. 2010 Apr 21;17(2):415-30.

7. Cochrane DR, Bernales S, Jacobsen BM, Cittelly DM, Howe EN, D'Amato NC, Spoelstra NS, Edgerton SM, Jean A, Guerroero J, Gómez F, Medicherla S, Alfaro IE, McCullagh E, Jedlicka P, Torkko KC, Thor AD, Elias AD, Protter AA, Richer JK. Role of the Androgen Receptor in Breast Cancer and Preclinical Analysis of Enzalutamide. Breast Cancer Research 2014 Jan 22;16(1): R7. doi: 10.1186/bcr3599. PMID: 24451109

8. D'Amato NC, Jacobsen BM, Gordon MA, Barton VN, Rogers TJ, Spoelstra NS, Babbs BL, Sartorius CA, Elias AD, Gertz J, Richer JK. Androgen receptor supports ER activity and genomic binding in breast cancer. 2016, submitted.

9. Elias A, Richer JK, LoRusso P, Peterson AC, Steinberg J, Mordenti J, Lopez C, Hudis C, Traina T. MDV3100-08: A phase 1 open-label, dose-escalation study evaluating the safety, tolerability, and pharmacokinetics of MDV3100 in women with incurable breast cancer. ASCO 2012, TPS668.

10. Traina TA, Yardley, DA, Patel M, Schwartzberg L, Elias A, Gucalp A, Peterson AC, Hannah A, Gibbons J, Khondker Z, Hudis CA, LoRusso P. A phase 1 open-label, dose-escalation study evaluating the safety, tolerability, and pharmacokinetics of enzalutamide (previously MDV3100) alone or in combination with an aromatase inhibitor in women with advanced breast cancer. SABCS 2013 PD3-6 (A938), poster discussion.

11. Traina TA, Yardley DA, Patel MR, Schwartzberg LS, Elias A, Gucalp A, Blaney ME, Gibbons J, Hudis CA, LoRusso P. A phase 1 open-label study evaluating the safety, tolerability, and pharmacokinetics of enzalutamide alone or combined with an aromatase inhibitor in women with advanced breast cancer. IMPAKT 2014 Breast Cancer Conference May 2014, Abstract 214.

12. Schwartzberg LS, Yardley DA, Elias A, Patel MR, Gucalp A, Burris HA, Peterson AC, Hannah AL, Blaney ME, Gibbons J, Tudor IC, Steinberg JL, LoRusso P, Infante JR, Hudis CA, Traina TA. Enzalutamide plus exemestane: a pilot study to assess safety, pharmacokinetics, and effects on circulating estrogens in women with advanced hormone-positive breast cancer. Proc ASCO 2014.

13. Elias AD, Burris HA, Patel MR, Schwartzberg LS, Richer JK, Kavalerchik E, Stopatschinskaja S, Gibbons J, Markova D, Steinberg JL, Traina TA. MDV3100-08: a phase I study evaluating the safety and pharmacokinetics of enzalutamide plus fulvestrant in women with advanced hormone receptor-positive breast cancer. Proc SABCS 2015, poster presentation.

14. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012 Sep 27; 367(13):1187-97.

15. Yeo B, Dowsett M. Neoadjuvant endocrine therapy: patient selection, treatment duration and surrogate endpoints. Breast 2015; 24 Suppl 2: S78-83.

16. Charehbili A, Fontein DB, Kroep JR, Liefers GJ, Mieog JS, Nortier JW, et al. Neoadjuvant hormonal therapy for endocrine sensitive breast cancer: a systematic review Cancer Treat Rev, 40 (2014), pp. 86–92.

17. Semiglazov VF, Semiglazov VV, Dashyan GA, Ziltsova EK, Ivanov VG, Bozhok AA, et al. Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. Cancer, 110 (2007), pp. 244–254.

18. von Minckwitz G, Untch M, Nuesch E, Loibl S, Kaufmann M, Kummel S, et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat, 125 (2011), pp. 145–156.

19. Kaufmann M, Hortobagyi GN, Goldhirsch A, Scholl S, Makris A, Valagussa P, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. J Clin Oncol, 24 (2006), pp. 1940–1949.

20. Dowsett M, Smith IE, Ebbs SR, Dixon JM, Skene A, Griffith C, et al. Short-term changes in Ki-67 during neoadjuvant treatment of primary breast cancer with anastrozole or tamoxifen alone or combined correlate with recurrence-free survival. Clin Cancer Res, 11 (2005), pp. 951s–958s.

21. M.J. Ellis MJ, C. Ma C. Letrozole in the neoadjuvant setting: the P024 trial. Breast Cancer Res Treat, 105 (Suppl. 1) (2007), pp. 33–43.

22. Ellis MJ, Tao Y, Luo J, A'Hern R, Evans DB, Bhatnagar AS, et al. Outcome prediction for estrogen receptor-positive breast cancer based on post neoadjuvant endocrine therapy tumor characteristics. J Natl Cancer Inst, 100 (2008), pp. 1380–1388.

23. Ellis MJ, Llombart-Cussac A, Feltl D, Dewar JA, Jasiówka M, Hewson N, Rukazenkov Y, Robertson JF. Fulvestrant 500 mg versus Anastrozole 1 mg for the First-Line Treatment of Advanced Breast Cancer: Overall Survival Analysis From the Phase II FIRSTStudy. J Clin Oncol. 2015 Nov 10;33(32):3781-7. doi: 10.1200/JCO.2015.61.5831. Epub 2015 Sep 14. PMID: 26371134

24. Robertson JF, Lindemann JP, Llombart-Cussac A, Rolski J, Feltl D, Dewar J, Emerson L, Dean A, Ellis MJ.

25. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: follow-up analysis from the randomized 'FIRST' study. Breast Cancer Res Treat. 2012 Nov;136(2):503-11. doi: 10.1007/s10549-012-2192-4. Epub 2012 Oct 13. PMID: 23065000

26. Simon, Richard. 'Optimal Two-Stage Designs for Phase II Clinical Trials', Controlled Clinical Trials, 1989, Volume 10, pages 1-10.

Principal Investigator: **Anthony Elias, MD**
COMIRB No: **16-1042**
Version Date: **March 6, 2020**

Study Title: **Randomized Phase II trial of preoperative fulvestrant with or without enzalutamide in ER+/ Her2- breast cancer**

You are being asked to be in a research study. This form provides you with information about the study. A member of the research team will describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

Why is this study being done?

This study plans to learn more about a combination of drugs called fulvestrant and enzalutamide and how they work together to treat your type of cancer. Fulvestrant is a standard treatment for your type of cancer. It works by blocking a hormone receptor on the cancer cells. Enzalutamide has been approved to treat other types of cancer and works to block a different hormone receptor. This study is looking at whether the two drugs can work together to help prevent the growth of cancer cells better than each drug could by itself.

You are being asked to be in this research study because you have ER+/ Her2- breast cancer that is at least stage T2, and you are planning to get local surgery to remove your cancer.

Other people in this study

Up to 44 people from your area will participate in this study.

Up to 81 people from around the country will participate in this study.

What happens if I join this study?

If you join the study, you will be asked to sign this consent form before you receive any study related tests or procedures. You will be given a copy of this form to keep and the original form will be kept at the clinic. Some of these procedures are the same as you would receive as standard of care treatment even if you did not take part in this trial. You can withdraw from the study at any time and without giving a reason. This will not affect the standard medical care you receive.

This study will have 2 different groups (arms) of research subjects like you. To decide which group you will be in, we will use a method of chance (randomized). This method is like flipping a coin or rolling dice. Each group will get slightly different care.

Combination Arm:

If you are in the Combination Arm, you will receive fulvestrant and the study drug enzalutamide. You will take 4 capsules of the enzalutamide by mouth every day.

Fulvestrant Arm:

If you are in the Fulvestrant Arm, you will receive fulvestrant alone.

You will know which arm you are in. If you are in an emergency, make sure you tell the emergency staff about this study. They can contact us, and we will give them all relevant information.

This next section is an overview of what will be expected of you, and what you can expect if you take part in this study.

Study visits and procedures

While you are taking part in this study, many of the tests and procedures that will be performed are standard of care for your disease. Some "research" procedures are performed just for this study and are identified below.

Screening – one to four weeks prior to entering study

- Sign informed consent – **research**
- Review medical history
- Collect archived tumor – **research**
- Breast Imaging
- Tumor imaging scan, such as a CT or MRI
- Performance status
- Height and weight
- Physical exam
- Breast exam
- Review adverse events
- Review medications
- Blood draw:
    - Standard of care tests including complete blood count, blood chemistry, and blood clotting
    - Tumor biomarkers test – **research**
    - Circulating tumor cells test– **research**
- Urine test for pregnancy if applicable
- Randomization – **research**

If you are pre- or peri-menopausal, you will receive injections of goserelin throughout the study as a standard part of treatment for your disease.

Treatment – *both Arms (Each cycle is 4 weeks long)*

Cycle 1/ Week 1/ Day 1

- Breast exam
- Review adverse events
- Review medications
- Blood draw (if not collected at screening):
  - Standard of care tests including complete blood count and blood chemistry
  - Tumor biomarkers test – **research**
- Tumor biopsy – **research**
- Fulvestrant injection (into your muscle)
- Receive 8 weeks of enzalutamide (if randomized to the Combination Arm). *You will take 4 capsules by mouth every day during this study.* – **research**

Cycle 1/ Day 15

- Fulvestrant (intra-muscular)

Cycle 2/ Week 5

- Breast exam
- Review adverse events
- Review medications
- Blood draw:
  - Standard of care tests including complete blood count, blood chemistry, and blood clotting, if clinically required
  - Tumor biomarkers test – **research**
- Tumor biopsy – **research**
- Fulvestrant injection (into your muscle)

Cycle 3/ Week 9

- Physical exam
- Breast exam
- Review adverse events
- Review medications
- Blood draw:
  - Standard of care tests including complete blood count and blood chemistry
  - Tumor biomarkers test – **research**
- Fulvestrant injection (into your muscle)
- Receive 8 weeks of enzalutamide (if applicable) – **research**

Cycle 4/ Week 13

- Breast exam
- Review adverse events
- Review medications

- Blood draw:
  - Standard of care tests including complete blood count and blood chemistry
  - Tumor biomarkers test – **research**
- Fulvestrant injection (into your muscle)

Pre-op

Week 17

- Breast imaging
- Physical exam
- Breast exam
- Review adverse events
- Review mediations
- Blood draw:
  - Standard of care tests including complete blood count, blood chemistry, and blood clotting, if clinically required
  - Tumor biomarkers test – **research**
  - Circulating tumor cells test– **research**

Post-op

Week 21

- Collect archived tissue and tumor biopsy at time of surgery – **research**
- Physical exam
- Breast exam
- Review adverse events
- Review medications
- Blood draw:
  - Standard of care tests including complete blood count and blood chemistry
  - Tumor biomarkers test – **research**
  - Circulating tumor cells test– **research**

Follow-up

After the last study visit, you will enter the follow-up period. The follow-up period will last until your disease progresses or for 5 years, whichever comes first. Study staff will follow-up with you at 6, 12, 18, and 24 months after the last study visit. They will also follow-up with you at 3, 4, and 5 years after the last study visit. Staff will follow-up with you at a scheduled clinic visit or may contact you by telephone.

Optional study procedures

Here are the optional parts of this study. ***Remember, no matter what you decide to do about this optional part of the study, you may still take part in the main study.*** If you decide to withdraw your consent for the optional parts, you can continue to take part in the main study, unless you withdraw your consent for the main study as well.

Following each optional procedure is a statement asking if you want to participate in the optional procedure. Please read the statement and think about your choice. After reading the sentence, please check "Yes" or "No" and initial next to your choice. If you have any questions, please talk to your doctor or nurse.

1. *Optional Consent for Future Contact*

   We would like your permission to allow us to contact you in the future to inform you about findings from this research and updates on this study on a periodic basis, when available.

   I give my permission for my study doctor (or someone he or she chooses) to contact me to inform me about findings from this research and updates on this study on a periodic basis, when available.

   ☐ Yes ☐ No _____Initials

2. *Optional Consent for Data and Specimen Banking for Future Research*

   Dr. Elias would like to keep some of the data, blood and tissue that is taken during the study but is not used for other tests. If you agree, the data and samples will be kept and may be used in future research to learn more about breast cancer. Your samples will be stored in the Breast Cancer Tissue Bank at the University of Colorado Denver. The research that is done with your data and samples is not designed to specifically help you. It might help people who have breast cancer and other diseases in the future. Reports about research done with your data and samples will not be given to you or your doctor. These reports will not be put in your health records. The research using your data and samples will not affect your care.

   The choice to let Dr. Elias keep the data and samples for future research is up to you. No matter what you decide to do, it will not affect the care that you will receive as part of the study. If you decide now that your data and samples can be kept for research, you can change your mind at any time and contact your study doctor to let him or her know that you do not want Dr. Elias to use your samples any longer, and they will no longer be used for research. Otherwise, they may be kept until they are used up, or until Dr. Elias decides to destroy them.

   When your data and samples are given to other researchers in the future, Dr. Elias will not give them your name, address, phone number or any other information that will let the researchers know who you are.

   Sometimes data and samples are used for genetic research (about diseases that are passed on in families). Even if your data and samples are used for this kind of research, the results will not be told to you and will not be put in your health records. Your data and samples will only be used for research and will not be sold. The research done with your data and samples may help to develop new products in the future, but there is no plan for you to be paid.

The possible benefits of research from your data and samples include learning more about what causes breast cancer and other diseases, how to prevent them and how to treat them. The greatest risk to you is the release of your private information. Dr. Elias will protect your records so that your name, address and phone number will be kept private. The chance that this information will be given to someone else is very small. There will be no cost to you for any data or sample collection and storage by Dr. Elias.

Please read each sentence below and think about your choice. After reading each sentence, check "yes" or "no" and initial next to your choice. If you have questions, please talk to your doctor or nurse. Remember, no matter what you decide to do about the storage and future use of your data and samples, you may still take part in the study.

1. I give my permission for my data, blood and tissue to be kept by Dr. Elias and stored in a central tissue bank at the University of Colorado Denver for future use by the study investigators.

   ☐ Yes ☐ No _____Initials

2. I give my permissions for my data, blood and tissue samples to be used for research about other health problems (for example: causes of heart disease, osteoporosis, diabetes).

   ☐ Yes ☐ No _____Initials

3. I give my permission for my study doctor (or someone he or she chooses) to contact me to inform me about findings from this research and updates on this study on a periodic basis, when available

   ☐ Yes ☐ No _____Initials

At the end of this consent form, you will also be asked to allow information collected from your specimens to be used. You need to agree to have information from these optional procedures to be used, or you cannot take part in these optional study procedures.

How long will I be on the study?

Your participation in the study will last for about 28 weeks. After the study procedures are done, the study team will follow up with you until your disease progresses or for 5 years, whichever comes first.

What are the possible discomforts or risks?

As with any study drug, side effects may occur while taking Enzalutamide and Fulvestrant. While taking part in this study, and being treated with Enzalutamide and Fulvestrant, you will be watched carefully for any side effects. Some side effects may go away after you stop taking the

study drug. Some side effects can be long lasting and may never go away or may even lead to death.

You should talk to your study doctor about any side effects or discomfort you may have. The study doctor may give you some medicine that will help with some side effects. The study doctor may also interrupt or discontinue the study drug.

You will be notified by your study doctor of any new side effects seen in other patients that occur during the time you are on the study. This may affect you wanting to continue in this research study.

Discomforts you may experience while in this study include:

Risks of Enzalutamide and Fulvestrant:

Enzalutamide:

Likely:

- Diarrhea
- Nausea
- Vomiting
- Fatigue or weakness
- Headache
- Feeling hot or flushed
- Increase in blood pressure

Less likely:

- Dizziness
- Memory impairment
- Restless leg syndrome
- Anxiety
- Nose bleeds
- Dry skin
- Itchy skin
- Skin rash
- Angina

Rare, but serious:

- Low white blood cell count, which may increase your risk of infection
- Seizures
- Epileptic seizures
- Hallucinations

Fulvestrant:

Likely:

- Fatigue or weakness
- Pain, including generalized, back, stomach, and injection site pain

- Headache
- Decrease in blood pressure
- Feeling hot or flushed
- Nausea
- Vomiting
- Constipation
- Diarrhea
- Bone pain
- Sore throat
- Cough

Less likely:

- Pelvic and chest pain
- Flu-like symptoms
- Fever
- Loss of appetite
- Anemia (low red blood cell count), which may cause tiredness or weakness
- Swelling in the hands and feet
- Joint swelling
- Dizziness
- Difficulty sleeping
- Numbness or tingling in the hands and feet
- Depression
- Anxiety
- Skin rash
- Sweating
- Urinary tract infection

Rare, but serious:

- Blood clots in your arms or legs that may reach the lungs
- Vaginal bleeding
- Low white blood cell count, which may increase your risk of infection
- Blood clot in the lungs (also known as pulmonary embolism)

Risks of having blood taken:

In this study, we plan to take about 2-3 tablespoons of blood from you at 6 different times. You may feel some pain when the needle goes into your vein, and you could have a bruise over the next few days.

Risks of biopsy:

In this study, we will take 2 biopsies from you. There are some risks to taking a biopsy. There is a small chance that you could get an infection where the needle goes in. You may also experience redness, swelling, minor bleeding or bruising at the site where the cut was made or the needle inserted. You may experience mild to moderate pain at the site of the needle puncture. There is also a small chance that you could have an allergic reaction to the

numbing medicine. After your skin heals up, you may have a small scar where we take the samples.

Archival tumor tissue:

A section will be taken from tumor tissue samples you may have had in the past. Since this has already been removed from you, there are no additional risks to you.

Risks of loss of confidentiality:

There is a risk that people outside of the research team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

Other possible risks include:

The particular treatment or procedures involved in this study may involve risks to the embryo or fetus which are currently unclear. Women of child-bearing potential should avoid getting pregnant while on this study.

This study may include risks that are unknown at this time.

What are the possible benefits of the study?

This study is designed for the researcher to learn more about your cancer and how the Enzalutamide and Fulvestrant affect this type of cancer. However, there is no guarantee that your health will improve if you join this study. Also, there could be risks to being in this study. If there are risks, these are described in the section describing the discomforts or risks.

Are there alternative treatments?

There may be other ways of treating your cancer. You have the following choices available to you:

- Getting treatment or care for your cancer without being in a study.
- Taking part in a different study.
- Get treatment only for your pain and symptoms, but no treatment for the cancer itself.
- You could also choose to get no treatment at all.

You should talk to your doctor about your choices. Make sure you understand all of your choices before you decide to take part in this study. You may leave this study and still have these other choices available to you.

Who is paying for this study?

This research is being paid for by The University of Colorado Cancer Center and the Department of Defense.

Will I be paid for being in the study?

You will not be paid to be in the study.

Will I have to pay for anything?

There are some medical treatments that you would get for your condition whether you were in this study or not, such as a biopsy or blood draw. You or your insurance will have to pay for these. There are other medical treatments that you will get because you are in this research study. We will pay for those. We will pay for biopsies and blood collection when they are not needed for your normal care. Otherwise, these procedures may be combined and charges will be sent to your insurance.

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled.

In addition, you have the right to change your mind at any point and write to the study doctor to not use your samples for research any longer.

If you leave this study, you will still receive your normal medical care. The only medical care that you will lose is the medical care you are getting as part of this study. You might be able to get that same kind of medical care outside of the study. Ask your study doctor.

If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them.

Can I be removed from this study?

The study doctor may decide to stop your participation without your permission if the study doctor thinks that being in the study may cause you harm, or for any other reason. You can still receive the study drug, if your doctor thinks that it is safe for you.

If you are taken out of the study, you will still receive your normal medical care.

What happens if I am injured or hurt during the study?

If you have an injury while you are in this study, you should call Dr. Anthony Elias immediately. His phone number is 720-848-1030 or 303-266-2059.

We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

Who do I call if I have questions?

The researcher carrying out this study is Dr. Anthony Elias. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Dr. Elias at 720-848-1030 or 303-266-2059. You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Dr. Elias with questions. You can also call the responsible Institutional Review Board (COMIRB). You can call them at 303-724-1055.

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

Who will see my research information?

The University of Colorado Denver (UCD) and its affiliated hospital(s) have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include:

- University of Colorado Denver
- University of Colorado Hospital

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the UCD and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information but confidentiality cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Anthony Elias, MD
Mailstop 8117
12801 E. 17th Ave.
Aurora, CO 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research subjects like you.
- People at the Colorado Multiple Institutional Review Board (COMIRB)
- The study doctor and the rest of the study team.

- The Independent Research Monitor, Dr. Elaine Lam, who is responsible for overseeing the safety of this research, and to report observations or findings to the IRB or designated institutional officials.
- Medivation and Astellas, the companies providing the drug, will see only coded information.
- Officials at the institution where the research is conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research.

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals, but we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator.

The investigator (or staff acting on behalf of the investigator) will use your information for the research outlined in this consent form. They will also make *all or some* **of the following health information about you collected in this study available to:** The West Clinic and Memorial Sloan Kettering Cancer Center.

Information about you that will be seen, collected, used and disclosed in this study:

- Name and Demographic Information (age, sex, ethnicity, address, phone number, etc.
- Portions of your previous and current Medical Records that are relevant to this study, including but not limited to Diagnosis(es), History and Physical, laboratory or tissue studies, radiology studies, procedure results
- Research Visit and Research Test records
- Tissue samples and the data with the samples
- Billing or financial information

Genetic Information Nondiscrimination Act (GINA)

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law will generally protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you, or when setting the terms of your employment.

All health insurance companies and group health plans must follow this law by May 21, 2010. All employers with 15 or more employees must follow this law as of November 21, 2009.

Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

What happens to Data, Tissue, Blood and Specimens that are collected in this study?

Scientists at the University of Colorado Denver and the hospitals involved in this study work to find the causes and cures of disease. The data, tissue, blood and specimens collected from you during this study are important to this study and to future research. If you join this study:

- The data, tissue, blood, or other specimens given by you to the investigators for this research no longer belong to you.
- Both the investigators and any sponsor of this research may study your data, tissue, blood, or other specimens collected from you.
- If data, tissue, blood, or other specimens are in a form that identifies you, UCD or the hospitals involved in this study may use them for future research only with your consent or Institutional Review Board (IRB) approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

HIPAA Authorization for Optional Additional Study Procedures

In this form, you were given the option to agree to additional, optional research procedures. You must also give us your permission, under HIPAA rules, to use and disclose the information collected from these optional procedures, as described above.

Some of these optional procedures may involve genetic testing or the use of your genetic information. Your genetic information will not be released to others.

If you decline to give us permission to use and disclose your information, you cannot take part in these optional procedures, but you can still participate in the main study. Please initial next to your choice:

_____ I give permission for my information, from the optional procedures I have agreed to above, to be used and disclosed as described in this section.

_____ I **do not** give permission for my information for any optional procedures to be used and disclosed; I understand that I will not participate in any optional procedures.

Agreement to be in this study and use my data

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I understand and authorize the access, use and disclosure of my information as stated in this form. I know that being in this study is voluntary. I choose to be in this study: I will get a signed and dated copy of this consent form.

Signature: _____ Date: _____

Print Name: _____

Consent form explained by: _____ Date: _____

Print Name: _____

If applicable, the signature line for witness is required for consent of non-reading subjects and consent using a short form.

Witness Signature: _____ Date: _____

Witness Print Name: _____

Witness of Signature ☐

Witness of consent process ☐