UCI 18-79

A Phase II Open Label Trial of Neoadjuvant Abemaciclib with Fulvestrant in Patients who Develop Localized Recurrence while on Adjuvant Endocrine Therapy with Molecular Evidence of Endocrine Resistance

Principal Investigator:
Ritesh Parajuli, MD
University of California Irvine/Division of Hematology/Oncology
101 The City Dr. South, Orange, CA 92868
(Phone) 714-456-8614
Email rparajul@hs.uci.edu
Breast Oncology

Sub-Investigator(s):
Rita Mehta, MD
Paul Coluzzi, MD
Andrea Nanci, M
Khosrow Mahdavi, MD
Department of Medicine/Division of Hematology/Oncology

John Butler, MD
Karen Lane, MD
Kari Kansal, MD
Erin Lin, MD
Department of Medicine/Division of Surgical Oncology

Biostatistician:
Argyrio Ziogas, MD
Principal Statistician
University of California, Irvine
222D Irvine Hall, Irvine, CA 92697
(Phone) 949-824-1587
Email aziogas@hs.uci.edu

Coordinating Center:
UC Irvine Chao Family Comprehensive Cancer Center
101 The City Drive South, Orange CA 92868
Contact: Nidhisha Patel, Clinical Research Manager
Phone: 714-509-2430
Email: uci1879@hs.uci.edu

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The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: _____

PI Signature: _____

Date: _____

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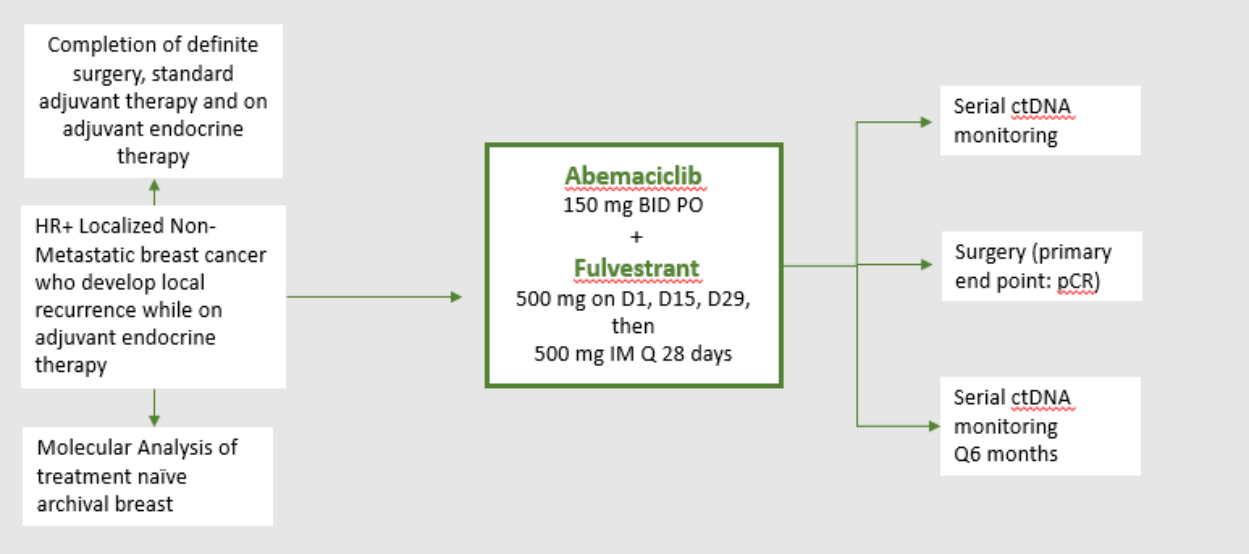
LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ER	Estrogen Receptor
H&P	History & Physical Exam
HRPP	Human Research Protections Program
ILD	Interstitial Lung Disease
IM	Intramuscularly
MBC	Metastatic Breast Cancer
MTD	Maximum Tolerated Dose
NGS	Next Generation Sequencing
ORR	Objective Response Rate
OS	Overall Survival
PCP	Primary Care Physician
pCR	Pathologic Complete Response
PD	Progressive Disease
PI	Principal Investigator
p.o.	per os/by mouth/orally
PR	Partial Response
PRBC	Packed Red Blood Cells
SAE	Serious Adverse Event
SD	Stable Disease
ULN	Upper Limit of Normal
WBC	White Blood Cells

STUDY SCHEMA



STUDY SUMMARY

Title	A Phase II Open Label Trial of Neoadjuvant Abemaciclib with Fulvestrant in Patients who Develop Localized Recurrence while on Adjuvant Endocrine Therapy with Molecular Evidence of Endocrine Resistance
Protocol Number	UCI 18-79
Phase	Phase 2
Methodology	Open-Label
Study Duration	5 years
Study Center(s)	Single-Center

Objectives	**Primary Objective:** To determine if Neo-adjuvant Abemaciclib and Fulvestrant improves a pathological complete response (pCR) in patients with Hormone Receptor positive patients with localized non-metastatic breast cancer who develop local recurrence while on adjuvant endocrine therapy with molecular evidence of endocrine resistance **Secondary Objectives:** 1. To determine the objective response rate (ORR) in the breast and/or the axillary lymph nodes 2. To determine if the combination of Abemaciclib and Fulvestrant increases the percentage of patients who undergo breast conserving surgery 3. Recurrence disease-free survival 4. Safety and Toxicity 5. To determine the percentage change in the Ki 67 from baseline to the treated specimen after breast surgery 6. To determine the preoperative endocrine prognostic index (PEPI) score as predictors of response to Neo-adjuvant Abemaciclib and Fulvestrant **Correlative Objectives:** 1. To determine if genomic analysis of patient matched breast tissue samples and serial mutational tracking of circulating tumor DNA can identify new mechanisms of endocrine resistance and how Abemaciclib overcomes endocrine resistance 2. To determine the mechanism of response or resistance to Abemaciclib 3. To determine biomarkers related to the Rb pathway
Number of Subjects	30
Diagnosis and Main Inclusion Criteria	**Inclusion Criteria** 1. Post-menopausal female patients who have given written informed consent 2. Histologically confirmed ER+ Breast Cancer 3. Patients must have localized non-metastatic breast cancer 4. Patients must have localized recurrence while on adjuvant endocrine therapy 5. Patients must have molecular evidence of endocrine resistance 6. ECOG performance 0-2 and adequate organ function **Exclusion Criteria** 1. Stage IV Metastatic Breast Cancer will be excluded 2. Patients with Her-2 positive and triple negative breast cancer will be excluded 3. Inflammatory breast cancer 4. Patients must have developed localized recurrence while on adjuvant endocrine therapy and hence newly diagnosed endocrine therapy naïve patients will be excluded 5. Patients without molecular evidence of endocrine resistance will be excluded 6. Prior treatment with any CDK 4/6 inhibitor and/or Fulvestrant will be excluded

Study Product(s), Dose, Route, Regimen	Abemaciclib 150mg twice daily administered orally in combination with Fulvestrant administered intramuscularly. The initial loading dose of Fulvestrant is 500mg on D1 and D15 of first cycle and then 500mg intramuscularly at D1 of each subsequent cycle (each cycle is 28 days). This combination therapy will continue until maximum response is obtained or patients develop unacceptable toxicity. Following therapy phase, patients will undergo definitive surgical treatment.
Duration of administration	The study will consist of a screening period of up to 28 days, a treatment period until maximum response per investigator discretion based on clinical and radiographic assessments, or until disease progression or unacceptable toxicity. The treatment phase will be followed by surgery, and follow up every 6 months until death or end of study at five years (whichever occurs first).
Statistical Methodology	Efficacy of the study will be measured by estimating the objective response rate (CR, PR) in the breast and/or the axillary lymph nodes or determining if the combination of Abemaciclib and Fulvestrant increases the percentage of patients who undergo breast conserving surgery. The latter will be measured by constructing 95% CI. We plan to use survival analysis methods such as Kaplan-Meier estimates of survival probability for univariate analysis and log rank tests in order to evaluate differences among distinct patient characteristics such as age group for recurrence or disease-free survival. For multivariate analysis we plan to use the Cox proportional hazards model in order to examine survival adjusted for a number of covariates. Safety and toxicity will be examined by the incidence of treatment-emergent, treatment-related adverse events (TRAEs), and serious adverse events (SAE). Consequently, side effects and adherence to the protocol will be closely monitored throughout the duration of the study. Interim analyses will be performed to assess the side effects. Contingency tables will be constructed to compare the proportion of patients with side effects by study characteristics (e.g. age, race ethnicity and other clinical and epidemiologic characteristics). Distributions of all data items will be generated and examined for the presence of outliers. This will be to assess the general form of the distributions, and to compute measures of central tendency and variability. Trellis graphics will be used for data display including histograms, boxplots, and Q-Q normal plots. In addition, we plan to examine if genomic analysis of patient-matched breast tissue samples and serial mutational tracking of circulating tumor DNA can identify new mechanisms of endocrine resistance and the way Abemaciclib overcomes this resistance. For the analyses of matched pair tissue data, we will use paired t tests or Wilcoxon sign rank statistical analysis in order to test differences in recurrent and treated breast tissue. We plan to measure absolute values and changes in circulating tumor DNA and correlate them with endocrine resistance. If serial monitoring of ctDNA can provide markers of resistance, we will quantify endocrine resistance as a composite outcome that will be computed as dichotomous variable if it happens (yes or no) and at what time interval during the study. We will start by using frequency table analysis to examine the relationship between resistance or sensitivity and specific mutations.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Breast cancer is one of the most common cancers in women. In 2012, there were approximately1.7 million new cases of breast cancer worldwide; since 2008, the worldwide incidence of breast cancer has increased by more than 20% and mortality has increased by 14% (Bray et al. 2013; Ferlay et al. 2013). While early stage disease is treatable, patients with metastatic breast cancer (mBC) have a median overall survival (OS) of only 2 to 3 years (Cardoso et al. 2012). The treatment for women diagnosed with hormone receptor positive (HR+) mBC includes endocrine therapy. In postmenopausal women, aromatase inhibitors (including anastrozole and letrozole) are recommended for the initial treatment of mBC, if not used in the adjuvant setting or if discontinued for at least 12 months (Cardoso et al. 2012). However, de novo or acquired resistance to adjuvant endocrine therapy and metastatic breast cancer remains an important clinical challenge.

CDK 4/6 Inhibitors in Metastatic Breast Cancer

Resistance to endocrine therapy in patients with HR+ Metastatic breast cancer is a major cause of treatment failure. Over activation of the Cyclin Dependent Kinase (CDK) pathway is an important mechanism of endocrine resistance. Cyclin D1 interacts with cyclin-dependent kinases
4 and 6 (hereafter CDK4 and CDK6) in an active protein complex that promotes cell proliferation (Velasco-Velazquez et al. 2011). Many HR+ breast cancers demonstrate an intact retinoblastoma tumor suppressive function, however, overexpression of cyclin D1 protein by oncogenic signaling occurs in approximately 30% to 50% of cancers. Cyclin D1 is regarded as the most frequently overexpressed gene in primary breast cancer, with amplification of the encoding gene, CCND1, occurring in approximately 15% of breast cancers (Casimiro et al. 2014). Therefore, CDK4 and CDK6 represent a potential therapeutic target for HR+ breast cancer. During the cell cycle, the G1 restriction point controls entry into S phase and is essential for proper regulation of cell proliferation (Sherr 1996; Ortega et al. 2002). CDK4 and CDK6 participate in a complex with the D-type cyclins to initiate progression through the G1 restriction point. The CDK4 and CDK6 - cyclin D1 complex regulates the G1 restriction point through phosphorylation and inactivation of the retinoblastoma (Rb) tumor suppressor protein, thereby promoting S phase entry. Alterations in this pathway occur frequently in human cancers and involve: 1) loss of functional CDK inhibitors through deletion or epigenetic silencing; 2) activating mutations and/or overexpression of CDK4 and CDK6 or the D-type cyclins; and 3) loss of functional Rb through mutation or deletion. Except for tumors with functional loss of Rb, which functions downstream of the CDK4 and CDK6 - cyclin D1 complex, most cancers are potentially sensitive to pharmacologic inhibition of CDK4 and CDK6. From a therapeutic standpoint, the goal of inhibiting CDK4 and CDK6 with a small molecule is to prevent cell cycle progression through the G1 restriction point, thus arresting tumor growth. Among postmenopausal women with hormone receptor-positive metastatic breast cancer, combinations of the AI letrozole with CDK 4/6 inhibitors (palbociclib, ribociclib, or abemaciclib) have demonstrated improved progression-free survival (PFS) relative to letrozole alone and have been approved by the US Food and Drug Administration (FDA) in this setting..

1.2 Study Agent(s) Background and Associated Known Toxicities

Abemaciclib is a selective and potent small molecule inhibitor of CDK4 and CDK 6. Abemaciclib is FDA approved in combination with an AI for the initial treatment of postmenopausal women with hormone receptor-positive, HER2-negative breast cancer. In the MONARCH 3 trial, the combination of abemaciclib with an AI (letrozole or anastrozole) was compared with AI monotherapy for the frontline treatment of women with advanced hormone receptor-positive, HER2-negative breast cancer. PFS, the primary endpoint of the trial, was increased with the combination compared with an AI alone (median not reached versus 14.7 months, respectively. Abemaciclib has been shown to combine effectively with fulvestrant. In the MONARCH 2 phase III trial, 669 patients who had progressed while receiving ET were randomly assigned to fulvestrant with or without the CDK 4/6-inhibitor abemaciclib. Those receiving abemaciclib experienced an improved PFS relative to those receiving fulvestrant alone (16.4 versus 9.3 months; HR 0.55, 95% CI 0.45-0.68). The ORR was higher in those receiving abemaciclib (48 versus 21 percent). The FDA in combination approves Abemaciclib with fulvestrant for women with progressive disease after prior endocrine therapy. Results from the phase II MONARCH 1 study, which enrolled 132 patients with a median of three prior lines of treatment (including one or two prior chemotherapy regimens in the metastatic setting), single- agent treatment with the novel CDK 4/6 inhibitor abemaciclib induced tumor response in 20 percent of patients, with a clinical benefit rate (stable or responding disease) of 42 percent, and median PFS of 6.0 months. The FDA has also approved abemaciclib as monotherapy for women with progressive disease after endocrine therapy and chemotherapy.

1.3 Other Agents

Fulvestrant is an ER antagonist that blocks ER dimerization and DNA binding, increases ER turnover, and inhibits nuclear uptake of the receptor. Fulvestrant has been approved in combination with either Palbociclib or Ribociclib or Abemacilcib in the treatment of patients with ER+ metastatic breast cancer.

1.4 Rationale

Neoadjuvant Endocrine Therapy:

Neo-adjuvant chemotherapy (NACT) refers to systemic treatment of breast cancer prior to definite surgical treatment. While all systemic therapy given for non-metastatic invasive breast cancer is intended to reduce the risk of distant recurrence, the purpose of administering it neoadjuvantly is to downstage the tumor, allow for less extensive surgery, improve cosmetic outcomes and reduce postoperative complications (1). By reducing the size of the primary tumor, preoperative therapy also allows for higher rate of breast conserving surgery. Achieving a complete pathologic response to Neo-Adjuvant chemotherapy has prognostic implications in patients with breast cancer (2, 3) and failure to achieve a complete pathologic response are associated with a high risk of local relapse.

Unlike Her-2+ and Triple negative breast cancers, HR+ breast cancers are less likely to respond to NACT (4-8). Chemotherapy can shrink HR+ tumors and facilitate better surgical outcomes, but is less likely to achieve a complete pCR in HR+ cancers, especially luminal A cancers than for more proliferative histology (9, 10). While historically neoadjuvant endocrine therapy (NET) has been reserved for patients with substantial comorbid health problems who would not tolerate chemotherapy, it is coming to be seen as a viable alternative for other patients, especially those with strong HR+ tumors that are strongly ER+. Tumors that are more likely to respond to NET have strong

HR expression (≥ 50% ER+ or an Allred score of 7 or 8) and a low proliferative index (Ki 67 < 10 or 15 %).

The standard of care options for Post-menopausal patient who develop localized or locally advanced recurrent HR+ Breast cancer while on adjuvant endocrine therapy remains to be surgical resection. The treatment depends on the type of local treatment they received at the initial diagnosis. Recurrence can happen after a lumpectomy and radiation or following mastectomy. Mastectomy is the surgical standard of care for most patients with a local recurrence following breast conserving surgery and radiation. Surgery in the form of wide local excision is recommended for post mastectomy chest wall recurrence. The role of radiation in the management of localized recurrence also depends upon if patients received adjuvant radiation at the initial diagnosis. Surgery and radiation in recurrent HR + breast cancer only address local control. Patients with recurrent breast cancer are at risk of developing metastatic breast cancer, have microscopic metastasis and many have evidence of endocrine resistance. Furthermore, extensive loco-regional recurrence is not amenable to surgical resection alone. Surgery and radiation does not address endocrine resistance nor does it treat microscopic metastasis. Hence, addressing endocrine resistance as well as adopting a targeted Neo-Adjuvant approach based on patient's tumor profiling and then treating them with the Abemaciclib and Fulvestrant to downstage the tumor, limit chemotherapy induced toxicity is the next logical step in the management of patients. These patients often land up getting Neo-Adjuvant chemotherapy. Few achieve a complete pathologic response and many are subjected to severe peri-operative complications. Hence, there continues to be an unmet medical need to develop alternate therapies that are less toxic and provide better outcomes. Neoadjuvant endocrine therapy can be an alternative option to chemotherapy in Hormone Receptor positive (HR+) tumors, particularly for postmenopausal women. Unlike in premenopausal women, available data suggest that NET is associated with similar response rates and rates of breast- conserving surgery (BCS) as NACT with lower toxicity, although survival data with NET are not yet available (11-15).

Resistance to endocrine therapy in patients with HR+ Metastatic breast cancer is a major cause of treatment failure. Cyclin-dependent kinases 4 and 6 (CDK 4 and 6) inhibition is proving to be an effective strategy in overcoming endocrine resistance. The data on the use of CDK 4/6 inhibitors with Fulvestrant or an Aromatase Inhibitor has been discussed in section 1.1 and 1.2. However, patients will eventually become resistant to CDK 4/6 inhibitors. Other than ER positivity, we do not fully understand the mechanism of sensitivity or resistance to CDK 4/6 inhibitors in ER+ MBC apart from Rb (Retinoblastoma gene) loss predicting for resistance. However, rather than waiting for endocrine resistance to develop in the adjuvant or the metastatic setting, identifying and targeting endocrine resistance in the Neo-adjuvant setting is expected to delay or prevent the development of endocrine resistance and hence improve patient outcomes. The concept for this proposal originated from real patient scenarios. We identified three patients in our institution that developed localized non-metastatic HR+ recurrent breast cancer while on adjuvant Anastrozole.

All three were treated with NACT and none achieved a complete pCR. Molecular analysis of the recurrent tissue harbored CCND1 amplification and ctDNA analysis showed ESR1 mutations in all of the three patients. Besides Estrogen receptor positivity, CCND1 amplification is one suggested biomarker that could predict response to CDK 4/6 inhibitors. Furthermore, the PALOMA studies showed that Fulvestrant is effective in patients with ESR1 mutation. We then hypothesized this cohort of patients with the

aforementioned genomic changes will benefit from a combination of a CDK 4/6 inhibitor and Fulvestrant.

Several ongoing trials are investigating the role of combination therapy including the combination of AIs with CDK 4/6 inhibitors (NeoMONARCH), PI3K inhibitors (LORELEI) and dual endocrine therapy (ALTERNATE).The NeoMONARCH study randomly assigned postmenopausal women with early stage HR+ breast cancer to Neoadjuvant therapy with Anastrozole, Abemaciclib or Anastrozole with Abemacilib. The study met its primary endpoint by showing that Ki-67 levels were significantly reduced in breast cancer cells from the 107 patients who received abemaciclib, either alone or in combination with anastrozole, compared with the 54 patients who received anastrozole only. Treatment with abemaciclib plus anastrozole led to a reduction in tumor size in most patients, as assessed by clinical and radiologic evaluation. This clearly showed that Abemaciclib works in the Neo-Adjuvant setting. While both CDK 4/6 inhibitors and Fulvestrant have been known to overcome endocrine resistance, a combination of Abemaciclib with Fulvestrant (as proposed in this trial) is expected to yield higher response rates, reduction in the ki-67 index and lead onto an improved pathologic complete response.

None of the clinical trials evaluating the combination of Neoadjuvant endocrine therapy with a CDK 4/6 inhibitor has addressed the unique cohort and the biology of endocrine resistance in such patients that is being proposed in this study. Identifying endocrine resistance in the Neo-adjuvant manner and targeting to improve patient outcomes is the fundamental goal of our study. Therefore, based on a clear unmet medical need, we plan to conduct a prospective, open-label Phase II study of Neo-Adjuvant Abemaciclib with Fulvestrant in post-menopausal patients who develop localized HR+ non-metastatic recurrence while on adjuvant endocrine therapy but with molecular evidence of endocrine resistance and longitudinally monitor ctDNA for evolving mutations. This personalized and targeted Neoadjuvant approach has the potential to demonstrate that Abemaciclib and Fulvestrant can increase pCR, reveal mechanisms of endocrine resistance and elucidate biomarkers of response or resistance to Abemaciclib. To the best of our knowledge, a study like this has not yet been conducted.

Potential Risk of Delaying Surgical Intervention:

The subjects enrolled in this trial will be treated with Abemaciclib and Fulvestrant until maximal response is obtained or until patients can tolerate it, following which they will undergo surgical resection with a curative intent. At any point in the study, if patients have signs and symptoms of metastasis, they will undergo systemic scans to seek for metastatic sites. Patients will be undergoing systemic scans to rule out metastasis prior to enrollment in the study. There remains a risk of disease progression while surgery is being delayed. However, Abemaciclib and Fulvestrant has currently been approved for the treatment of metastatic ER+ breast cancer now. We believe that patients will have a relatively lower risk of disease progression while on this treatment since this regimen is standard of care in treating ER+ MBC and also since patients will undergo systemic scans prior to enrollment. Furthermore, the risk of delaying surgical intervention will be described in the informed consent provided to research participants.

1.5 Correlative Studies

Molecular analysis in the form of Next Generation Sequencing will be done on the treatment naïve archival breast tissue, on the breast tissue at the time of recurrence and on the surgical specimen. Blood will be collected as well for analysis of ctDNA before enrollment, every 3 months while on treatment and then every 6 months (after definitive surgery) until the end of the study at five years. The molecular analysis by Next

generation sequencing (NGS) will be done by Tempus using their standard platform. No identifiable information for the correlative studies will be sent to Tempus. Only subject ID and study site information will be provided on requisition forms, kit labels, and any reports (e.g. pathology report, progress note) are being submitted to Tempus.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To determine if Neo-adjuvant Abemaciclib and Fulvestrant improves a pathological complete response in patients with Hormone Receptor positive patients with localized non- metastatic breast cancer who develop local recurrence while on adjuvant endocrine therapy with molecular evidence of endocrine resistance

2.2 Secondary Objectives

2.2.1 To determine the objective response rate (ORR) in the breast and/or the axillary lymph nodes

2.2.2 To determine if the combination of Abemaciclib and Fulvestrant increases the percentage of patients who undergo breast conserving surgery

2.2.3 Recurrence disease-free survival

2.2.4 Safety and Toxicity

2.2.5 To determine the percentage change in the Ki 67 from baseline to the treated specimen after breast surgery

2.2.6 To determine the preoperative endocrine prognostic index (PEPI) score as predictors of response to Neo-adjuvant Abemaciclib and Fulvestrant

2.3 Correlative Objectives

2.3.1 To determine if genomic analysis of patient matched breast tissue samples and serial mutational tracking of circulating tumor DNA can identify new mechanisms of endocrine resistance and how Abemaciclib overcomes endocrine resistance

2.3.2 To determine the mechanism of response or resistance to Abemaciclib

2.3.3 To determine biomarkers related to the Rb pathway

2.4 Endpoints

The primary endpoint is pathological complete response (pCR) as defined by no evidence of tumor cells in the final surgical specimen
The secondary endpoints are ORR per RECIST 1.1 criteria, recurrence disease-free and incidence of AEs

3.0 PATIENT ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

3.1.1 Patients must have a diagnosis of HR+ breast cancer. To fulfill the requirement of HR+ disease, a breast cancer must express, by immunohistochemistry (IHC), at least one of the hormone receptors (ER, progesterone receptor [PgR]) as defined in the relevant American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) Guidelines (Hammond et al. 2010):

- For ER and PgR assays to be considered positive, ≥1% of tumor cell nuclei must be immunoreactive by immunohistochemistry (IHC) (Hammond et al. 2010).

3.1.2 Patients must have Loco regional breast cancer (Stage I, Stage II and stage III per AJCC 8th edition criteria for staging of breast cancer)

3.1.3 Patients must have localized recurrence while on adjuvant endocrine therapy

3.1.4 Patients must have any known molecular evidence of endocrine resistance by next generation sequencing

3.1.5 Age ≥ 18 years.

3.1.6 ECOG performance status 0-1

3.1.7 Have post-menopausal status as defined by following:

- Prior bilateral oophorectomy
- Age ≥ 60 years
- Age < 60 and amenorrheic (non-treatment-induced amenorrhea secondary to tamoxifen, toremifene, ovarian suppression, or chemotherapy) for at least 12 months. Follicle-stimulating hormone (FSH) and estradiol must be in the postmenopausal range.

3.1.8 Have at least one measurable disease as defined per RECIST 1.1

3.1.9 Adequate organ and marrow function as defined below:

- Hemoglobin*	> 8 g/dL
- Absolute neutrophil count	≥ 1,500/mcL
- Platelets	≥ 100,000/mcl
- Total bilirubin	≤ 1.5 X institutional ULN

Patients with Gilbert's syndrome with a total bilirubin ≤2.0 times ULN and direct bilirubin within normal limits are permitted

- AST (SGOT)/ALT (SPGT)	≤ 2.5 X institutional ULN
- Creatinine	≤ 1.5 X institutional ULN

**Patients may receive transfusion of packed red blood cells (PRBC) to achieve this hemoglobin level at the discretion of the investigator; however, initial study drug treatment must not begin earlier than the day after the PRBC transfusion.*

3.1.10 Able to swallow oral medications

3.1.11 Patients who received adjuvant radiotherapy must have completed and fully recovered from the acute effects of radiotherapy. A washout period of at least 14 days is required between end of radiotherapy and screening for the study.

3.1.12 Patients who received chemotherapy must have recovered (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≤1) from the acute effects of chemotherapy except for residual alopecia or Grade 2 peripheral neuropathy prior to enrollment. A washout period of at least 21 days is required between last chemotherapy dose and enrollment (provided the patient did not receive radiotherapy).

3.1.13 Any known markers of response or resistance to CDK 4/6 inhibitors to be present in the biopsy specimen

3.1.14 If patients have been treated with prior Neo-Adjuvant chemotherapy at the time of primary diagnosis and not at the time of recurrence, they will be included in the study.

3.1.15 Must be able to sign a written informed consent, are reliable, willing to be available for the duration of the study and are willing to follow study procedures

3.2 Exclusion Criteria

3.2.1 Stage IV metastatic breast cancer

- This study will utilize the American Joint Committee on Cancer (AJCC) staging system, eight edition that provides a strategy for grouping patients with respect to prognosis. The AJCC has designated staging by TNM classification. The researchers will also review tumor size, lymph node status, and estrogen-receptor and progesterone-receptor levels in the tumor tissue.

3.2.2 Patients with HER2 positive and triple negative breast cancer

- To fulfill the requirement of HER2- and Triple negative disease, a breast cancer must not demonstrate, at initial diagnosis or upon subsequent biopsy, overexpression of HER2 or should not express ER or PR receptors by either IHC or in-situ hybridization (ISH) as defined in the relevant ASCO/CAP guidelines (Wolff et al. 2013).

3.2.3 Inflammatory breast cancer

3.2.4 Newly diagnosed endocrine naïve patients

3.2.5 No molecular evidence of endocrine resistance

3.2.6 Prior treatment with any CDK 4/6 inhibitor and/or Fulvestrant

3.2.7 Pre-menopausal women

3.2.8 Are currently receiving an investigational drug in a clinical trial or participating in any other type of medical research judged not to be scientifically or medically

compatible with this study. If a patient is currently enrolled in a clinical trial involving non-approved use of a device, then agreement with the principal investigator is required to establish eligibility

3.2.9 Have had major surgery within 14 days prior to enrollment to allow for post-operative healing of the surgical wound

3.2.10 Have initiated bisphosphonates or approved RANK ligand therapy for breast cancer with osseous metastasis, if patients are received Zolendronic acid or Denosumab in the adjuvant manner then such patients will be allowed participate

3.2.11 Have serious preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study (for example, history of major surgical resection involving the stomach or small bowel or preexisting Crohn's disease or ulcerative colitis , interstitial lung disease, severe dyspnea at rest, any pre-existing chronic condition resulting in baseline grade 2 or higher diarrhea)

3.2.12 Have a personal history of any of the following conditions: syncope or cardiovascular etiology, ventricular tachycardia, ventricular fibrillation or sudden cardiac arrest

3.2.13 Have a history of any other cancer (except for non-melanoma skin cancer or carcinoma in situ of the cervix) unless in complete remission with no therapy for a minimum of three years or have received an autologous or allogeneic stem-cell transplant

3.2.14 Have an active bacterial or fungal infection or a detectable viral infection (for example HIV or viral hepatitis). Screening is not required for enrollment

3.2.15 Recent therapy with a biologic agent or a monoclonal therapy is excluded. Wash out of at least three half-lives of monoclonal antibody would be required to be enrolled.

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

4.1.1 Abemaciclib will be administered orally at the dose of 150 mg twice daily. Fulvestrant will be administered intramuscularly at an initial loading dose of 500mg on days 1 and 15 of the first cycle and then 500 mg intramuscularly every first day of each subsequent cycle. One cycle is 28 days.

REGIMEN DESCRIPTION				
Agent	**Dose**	**Route**	**Schedule**	**Cycle Length**

Abemaciclib	150 mg	Oral (PO)	BID	4 weeks (28 days)
Fulvestrant	500 mg	IM	C1D1, C1D15, and D1 of each subsequent cycle	

4.1.2 Supportive Care Guidelines

Necessary supportive measures for optimal medical care will be given throughout the study including antidiarrheal, blood components etc. Additional care will be administered as indicated by the treating physician and the subject's medical need. All the concomitant medications and supportive therapy administered during the 30 days prior to the first dose until 30 days after the last dose must be recorded in OnCore eCRF.

4.2 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events table (Section 5.4). Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 5.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

4.2.1 Abemaciclib Dose Modification and Management

Please refer to the following tables for dose modifications for adverse reactions related to abemaciclib. If dose reduction is necessary, decrease the dose by 50 mg at a time. Discontinue abemaciclib for patients unable to tolerate 50 mg twice a day (BID).

Abemaciclib Dose Modifications for Adverse Events

Dose Level	Abemaciclib dose in combination with fulvestrant
Recommended Starting Dose	150 mg
First Dose Reduction	100 mg
Second Dose Reduction	50 mg
Third Dose Reduction	Not applicable

Hematologic Toxicities

Hematologic toxicities including neutropenia, leukopenia, anemia, and thrombocytopenia have been observed in patients treated with abemaciclib, and causality has been established. Severe (Grade 3 and 4) neutropenia was observed in patients receiving abemaciclib. Patients should be monitored closely for signs of infection, anemia, and bleeding.

Hematologic Toxicity Dose Management Guidelines
Monitor complete blood counts prior to the start of abemaciclib therapy, every 2

weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.	
CTCAE Grade	**Action**
Grade 1-2	No dose modification required
Grade 3	Suspend dose until toxicity resolves to ≤Grade 2. Dose reduction is not required.
Grade 3, recurrent, or Grade 4	Suspend dose until toxicity resolves to ≤Grade 2. Resume at next lower dose.

If blood cell growth factors are required, suspend abemaciclib dose for at least 48 hours after the last dose of blood cell growth factor and until toxicity resolves to ≤Grade 2. Resume at next lower dose unless already performed for the toxicity that led to the use of the growth factor. Growth factor use as per current treatment guidelines.

Hepatic Toxicities

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation are considered as ADR with the use of abemaciclib. The following information in Table 3 must be included in investigator-sponsored protocols for hepatic monitoring:

Hepatic Toxicity Dose Management Guidelines	
Monitor ALT prior to the start of abemaciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.	
CTCAE Grade for ALT and AST	**Action**
Grade 1 (>ULN-3.0 x ULN), Grade 2 (>3.0-5.0 x ULN), WITHOUT increase in total bilirubin above 2 x ULN	No dose modification required
Persistent or Recurrent Grade 2, or Grade 3 (>5.0-20.0 x ULN), WITHOUT increase in total bilirubin above 2 x ULN	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Elevation in AST and/or ALT >3 x ULN WITH total bilirubin >2 x ULN, in the absence of cholestasis	Discontinue abemaciclib
Grade 4 (>20.0 x ULN)	Discontinue abemaciclib

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. If a study patient experiences elevated ALT 5×ULN and elevated TBL 2×ULN, or ALT 8×ULN, liver tests, including ALT, AST, TBL, direct bilirubin, gamma-glutamyl transferase (GGT), and creatine phosphokinase (CPK), should be repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator, based on the hepatic monitoring tests below in Appendix B.

Diarrhea

At enrollment, patients should receive instructions on the prompt management of diarrhea. In the event of diarrhea, supportive care measures should be initiated as early as possible. These include the following:

- At the first sign of loose stools, the patient should initiate antidiarrheal therapy (e.g. loperamide) and notify the investigator for further instructions and appropriate follow up.
- Patients should also be encouraged to drink fluids (e.g., 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.
- Refer to table below for additional information for diarrhea management and dose modification.

Diarrhea Dose Management Guidelines	
At the first sign of loose stools, start treatment with antidiarrheal agents, such as loperamide.	
CTCAE Grade	**Action**
Grade 1	No dose modification required
Grade 2	If toxicity does not resolve within 24 hours to ≤ Grade 1, suspend dose until resolution. No dose reduction is required.
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	Suspend dose until toxicity resolves to ≤Grade 1. Resume at next lower dose.
Grade 3 or 4 or requires hospitalization	

Dose level reductions should be made in 50 mg increments. For example, if the starting dose of abemaciclib for a study is 150 mg q12 hours, dose reduction 1 would be 100 mg q12 hours, dose reduction 2 would be 50 mg q12 hours.

General Guidance for Interstitial lung disease (ILD)/Pneumonitis events

Interstitial lung disease (ILD) / pneumonitis has been identified as an adverse drug reaction for abemaciclib. Adverse events reported included events such as interstitial lung disease, pneumonitis, obliterative bronchiolitis, organizing pneumonia, pulmonary fibrosis. The majority of events were Grade 1 or Grade 2 with serious cases and fatal events reported.

Monitor for clinical symptoms or radiological changes indicative of ILD/pneumonitis and please ask patients to report any new or worsening pulmonary symptoms. Symptoms may include hypoxia, cough, dyspnea, or interstitial infliltrates on radiologic exams.; these symptoms should be investigated and treated as per local clinical practice and/or guidelines (including corticosteroids as appropriate). Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations. Investigations may include imaging such as high resolution computer tomography (HRCT), broncheoalveolar lavage (BAL), and biopsy as clinically indicated (see also Table).

Interstitial Lung Disease (ILD)/Pneumonitis

ILD/Pneumonitis Dose Management Guidelines	
CTCAE Grade	**Action**
Grade 1-2	No dose modification required
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to ≤Grade 1. Resume at next lower dose.
Grade 3-4	Discontinue abemaciclib

Non-hematological Toxicities (excluding Diarrhea, ALT Increased, and ILD Pneumonitis)

Non-Hematological Toxicity Dose Management Guidelines (excluding Diarrhea, ALT

Increased, and ILD Pneumonitis)	
Event	**Action**
Grade 1-2	No dose modification required
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or ≤Grade 1. Resume at next lower dose.
Grade 3-4	

Note: Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular transporters without affecting glomerular function (as measured by iohexol clearance). In clinical studies, increases in serum creatinine occurred within the first month of abemaciclib dosing, remained elevated but stable through the treatment period, were reversible upon treatment discontinuation, and were not accompanied by changes in markers of renal function, such as blood urea nitrogen (BUN), cystatin C, or calculated glomerular filtration rate based on cystatin C.

4.2.2 Dose Suspension and Cycle Delays

Both dose suspension (within a cycle) and cycle delay are permitted. Study treatment may be held up to 14 days within a cycle or at start of next cycle to permit sufficient time for recovery from the toxicity. Patients not recovering from toxicity within 14 days should be considered for discontinuation at the discretion of the investigator. In exceptional circumstances, a delay >14 days is permitted upon agreement with the principal investigator (PI).

A delay of a cycle due to holiday, weekend, bad weather, or other unforeseen circumstances will be permitted for a maximum of 7 days and not counted as a protocol deviation. In exceptional circumstances, a delay >7 days is permitted upon agreement with PI.

4.3 Fulvestrant Dose Modification and Management

4.3.1 Guidelines for Use in Patients with Hepatic Impairment:

A dose of 250mg is recommended for patients with moderate hepatic impairment (Child-Pugh class B). Faslodex has not been evaluated in patients with severe hepatic impairment (Child Pugh class C).

4.3.2 Guidelines for Use in Patients with Renal Impairment:

Negligible amounts of Fulvestrant are eliminated in the urine. No adjustment is recommended.

4.4 Concomitant Medications/Treatments

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates

All treatments that the investigator considers necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

All the concomitant medications and supportive therapy administered during the 30 days prior to the first dose until 30 days after the last dose must be recorded on the appropriate case report form (CRF).

Abemaciclib is predominantly cleared by oxidative metabolism via CYP3A4. Clinical drug interaction studies with a CYP3A inhibitor and CYP3A inducer significantly altered the PK of abemaciclib and its circulating major metabolites.

CYP3A Inducers

Avoid concomitant use of CYP3A inducers and consider alternative agents.

CYP3A Inhibitors

Avoid concomitant use of strong CYP3A inhibitors (for example, voriconazole) and use caution with coadministered moderate (for example, ciprofloxacin) or weak (for example, ranitidine) CYP3A inhibitors. If coadministration with a strong CYP3A inhibitor is unavoidable, reduce the abemaciclib dose to 100 mg twice daily or, in the case of ketoconazole, reduce the abemaciclib dose to 50 mg twice daily. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the abemaciclib dose to 50 mg twice daily. Avoid grapefruit or grapefruit juice. If a CYP3A inhibitor is discontinued, increase the abemaciclib dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor

General Guidance for use of Radiotherapy in Combination with Abemaciclib

Limited data are available with abemaciclib and radiotherapy or alternate dosing schedules (e.g. induction phase). Thus, caution should be exercised with administering abemaciclib with radiotherapy.

4.4.1 Palliative Medicine and Supportive Care

In the event patients develop adverse events requiring palliative care, investigator will refer patient to primary care physician (PCP).

4.3.2 Supportive Management for Diarrhea in Patients Receiving Abemaciclib

Patients should receive instructions on the management of diarrhea. In the event of diarrhea, supportive measures should be initiated as early as possible. These include the following:

- At the first sign of loose stools, the patient should initiate anti-diarrheal therapy (e.g., loperamide) and notify the investigator for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (e.g., 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.
- If diarrhea does not resolve with anti-diarrheal therapy within 24 hours to at least Grade 1 (per CTCAE v 5.0), study abemaciclib treatment should be suspended until diarrhea is resolved to at least Grade 1.
- When abemaciclib treatment recommences, dosing should be adjusted as outlined in Section 4.2.1. In severe cases of diarrhea, the measuring of

neutrophil counts and body temperature and proactive management of diarrhea with antidiarrheal agents should be considered.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia, broad-spectrum antibiotics such as fluoroquinolones should be considered. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be carefully monitored and given intravenous fluid and electrolyte replacement as clinically indicated.

4.5 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until:

- Maximum response (per investigator discretion based on clinical and/or imaging assessments) is obtained OR
- Disease progression as defined radiographic progression by RECIST v1.1 criteria OR death OR symptomatic progression as clinically determined by the treating physician
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

4.6 Duration of Follow Up

Patients will be followed every 6 months after surgery for ctDNA blood collection. The follow up phase will continue until study completion at 5 years or until death, whichever occurs first.

4.7 Removal of Patients from Protocol Therapy

Patients will be removed from therapy when any of the criteria listed in Section 5.5 apply. Notify UCI CFCCC via secure email (rparajul@hs.uci.edu and uci1879@hs.uci.edu), and document the reason for study removal and the date the patient was removed in OnCore. The patient should be followed-up per protocol.

4.8 Patient Replacement

Patients will not be replaced

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained as long as these assessments are completed within 28 days prior to registration.

All screening procedures must be performed within 28 days prior to registration unless otherwise stated. The screening procedures include:

5.1.1 **Informed Consent**

5.1.2 **Screening Confirmation**

Patient information should be entered into Oncore within 1 business day of consent. Site is responsible for assigning subject ID. Subject IDs should follow a format with the unique site code followed by sequential patient ID. For example, Site Code-Sequential Number (i.e. for first patient the subject ID will be 01-01). Refer to Oncore SOP for Oncore data entry instructions.

5.1.3 **Medical history**

Complete medical and surgical history

5.1.4 **Demographics**

Age, gender, race, ethnicity

5.1.5 **Review subject eligibility criteria**

5.1.6 **Review previous and concomitant medications**

5.1.7 **Physical exam**

5.1.8 **Vital signs, height and weight**

Temperature, pulse, respirations, blood pressure, weight and height (height only at screening)

5.1.9 **ECOG Performance status**

Refer to Appendix A

5.1.10 **Hematology**

Complete blood count (CBC) with differential

5.1.11 **Blood draw for correlative studies**

Blood collection for ctDNA.

5.1.12 **Serum chemistries**

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT, AST, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin.

5.1.13 **Tumor assessment**

To be performed with computed tomography (CT) of the chest (preferred with IV contrast) and abdomen/pelvis (preferred with IV and oral contrast) to rule out metastasis. CT abdomen/pelvis may be replaced with MRI Abdomen/pelvis (preferred with IV contrast) per clinical judgement of the treating physician. An MRI of the breast will also be required for RECIST 1.1 baseline assessment. Additional imaging is indicated at baseline if there is clinical suspicion for other organ involvement (i.e. MRI or CT brain and bone scan). Imaging is to be performed at baseline within 28 days of starting treatment

5.2 Registration Procedures

The below items must be reviewed and confirmation of eligibility must be completed by the PI and CRM prior to registration:

- Signed Informed consent
- Physical exam and complete medical and surgical history
- All screening labs
- Signed eligibility criteria

Items must be reviewed by the PI and CRM at least 3 business days before planned treatment start date.

5.3 Procedures During Treatment

5.3.1 Prior to Each Treatment Cycle

- Physical exam, vital signs
- Hematology
- Serum chemistries
- Adverse events
- Study drug accountability
- Review previous and current concomitant medications

Site must maintain an accurate and timely record of dispensing of study drug to subject, and receipt of all study drug and pill diaries.

5.3.2 Within 30 days after treatment termination

- Physical exam, vital signs
- Hematology
- Serum chemistries
- Adverse Events
- Review previous and current concomitant medications

5.2.3 Tumor Assessments

MRI breast to be completed every 12 weeks (+/- 7 days) during treatment phase

5.4 Follow-up Procedures

Patients will be followed every 6 (+/- 14 days) months after surgery until patient comes off study due to study completion at 5 years, death, or withdrawal, whichever comes first

- Blood collection for ctDNA

5.5 Time and Events Table

If baseline evaluations are conducted within 1 week prior to administration of protocol therapy, those assessments do not need to be repeated. Scans must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Baseline/Screening	**Treatment Phase**		**Post-discontinuation**		
	-28 to -1 days	**Cycle 1**	**Subsequent cycles**	**End of Treatment**	**Surgery**	**Follow-up**

		D1 (-3d)	D15 (±3d)	D1 (-3d)	Within 30 days of last dose prior to surgery		Every 6 months (±14d)
Assessment							
Informed Consent	X						
History and PE	X	X		X	X		
Vital Signs	X	X	X	X	X		
Baseline medical and oncology history	X						
Concomitant Medications	X	X		X	X		
ECOG Performance Status	X	X		X	X		X
Adverse Events		X		X	X		
Tumor Measurements	X						
CT CAP or CT chest/MRI Abd/Pelvis[1]	X						
MRI Breast	X	X Every 12 weeks (±7d) after first dose until maximum response or progression, whichever occurs first					
CBC w/diff	X	X	X	X	X		
CMP	X	X	X	X	X		
Postmenopausal Confirmation	X						
ctDNA (correlative study)	X			X[2]			X
Biopsy[3]					X		
Tissue Submission	X				X	X	
Administer Abemaciclib		X	X	X			
Administer Fulvestrant		X	X	X			
Study Drug Accountability				X	X		

[1] CT Chest, abdomen and pelvis with contrast or CT chest/MRI Abdomen, Pelvis is required at screening to rule out metastasis
[2] Every 3 months during treatment

[3] A fresh biopsy at time of progression is mandatory if clinically feasible.

5.6 Removal of Subjects from Study

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.5.1 Patient voluntarily withdraws from treatment (follow-up permitted);

5.5.2 Patient withdraws consent (termination of treatment and follow-up);

5.5.3 Patient is unable to comply with protocol requirements;

5.5.4 Patient demonstrates disease progression (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator);

5.5.5 Patient experiences toxicity that makes continuation in the protocol unsafe;

5.5.6 Treating physician judges continuation on the study would not be in the patient's best interest;

5.5.7 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

5.5.8 Lost to follow-up. If a research subject cannot be located to document survival after 3 attempts including 1 mailed certified letter, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented and approved by the Data Monitoring Committee.

6.0 Measurement of Effect

6.1 Pathologic Complete Response (pCR)

No histologic evidence of microscopic invasive tumor at the primary tumor site in the surgical specimen (ypT0 or ypTis).

6.2 Antitumor Effect- Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

6.2.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with study drug.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.2.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (CT, MRI, x-ray) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions

Target lesions. All measurable lesions up to a maximum of 3 lesions per organ and 6 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 6 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

6.2.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible

to the beginning of treatment and never more than 28 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Measurements should be performed on schedule even in the event of study treatment delay or omission.

Imaging delays due to patient deterioration will not be considered a protocol deviation.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. MRI is also acceptable in certain situations (e.g. for body scans). Scans will be done within 28 days prior to cycle 1 and after that every 8 weeks (+/- 7 days) until end of treatment.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

6.2.4 Response Criteria

6.2.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

6.2.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

6.2.5 Duration of Response

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

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

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

6.2.6 Objective Response Rate

ORR is defined as the percentage of patients who have achieved an objective confirmed overall complete response (CR) or partial response (PR) based on RECIST version 1.1 guidelines.

6.2.7 Recurrence Disease Free Survival

Recurrence disease free survival will be defined as the time from surgery until patient develops recurrence.

6.3 Safety/tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 5.0 for reporting of non-hematologic adverse events (http://ctep.cancer.gov/reporting/ctc.html) and modified criteria for hematologic adverse events (Appendix #/letter).

7.0 ADVERSE EVENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will use CTCAE v 5.0 to assign AE severity grades. Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Eli Lilly Pharmaceuticals to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient to discontinue the investigational product before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is otherwise explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical trials, because the purpose of the clinical trial is to establish drug effect.

After the ICF is signed, study site personnel will record via OnCore eCRF the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure, investigational product, via OnCore eCRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment taking into account the disease, concomitant treatment or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, study device and/or study procedure and the AE.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a patient's investigational product is discontinued as a result of an AE, study site personnel must report this to Eli Lilly Pharmaceuticals via Eli Lilly's IIR Portal for Trial Management or via fax, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

7.1 Definitions

7.1.1 Event Definition

Adverse event (AE) - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Unexpected Adverse Event [Modified from the definition of unexpected adverse drug experience in FDA regulations at 21 CFR 312.32 (a)] – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Serious Adverse Event (SAE) [21 CFR 312.32] - Defined as any expected or unexpected adverse event that result in any of the following outcomes:

- Death
- Is life-threatening experiences (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization equal or greater than 24 hours)) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unanticipated problem (UP) - Any incident, experience or outcome that meets all three of the following criteria:

1. Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**

3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

Protocol Violation- A protocol violation is an accidental or unintentional change to or noncompliance with the IRB-approved protocol that increases risk or decreases benefit and/or affects the subject's rights, safety, welfare, and/or the integrity of the data. Examples of incidents that may be considered violations include: enrolling a participant who does not meet the inclusion criteria; obtaining verbal consent before the initiation of study procedures when the IRB requires signed, written informed consent; and failure to collect screening labs before initiation of study procedures [Reference: Policy #57 UCI HRPP Policy and Procedure Glossary].

Protocol Deviation- A protocol deviation is an accidental or unintentional change to the research protocol that does not increase risk or decrease benefit or have a significant effect on the participant's rights, safety or welfare, or on the integrity of the data. Deviations may result from the action of the participant, researcher, or staff. Examples: a rescheduled study visit, an omitted routine safety lab for a participant with previously normal values; or failure to collect an ancillary self-report questionnaire data (e.g., quality of life) [Reference: Policy #57 UCI HRPP Policy and Procedure Glossary].

Characteristics and Severity of Adverse Events

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE v5 is available at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

If no CTCAE grading is available, the severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.

Moderate (grade 2): the event causes discomfort that affects normal daily activities.

Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.

7.1.2 Characteristics and Severity of Adverse Events

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE v5 is available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

If no CTCAE grading is available, the severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.

Moderate (grade 2): the event causes discomfort that affects normal daily activities.

Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.

Life-threatening (grade 4): the patient was at risk of death at the time of the event.

Fatal (grade 5): the event caused death.

Attribution of the AE:

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

7.1.3 Serious Adverse Events

A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

7.1.3.1 Results in death.

If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

7.1.3.2 Is life-threatening.

(the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).

7.1.3.3 Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

7.1.3.4 Results in persistent or significant disability or incapacity.

7.1.3.5 Is a congenital anomaly/birth defect

7.1.3.6 Is an important medical event

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

7.2 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v5).

Step 2: Grade the adverse event using the NCI CTCAE v5.

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as per section 7.3.2:

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

1. the current known adverse events listed in the Agent Information Section of this protocol;
2. the drug package insert;
3. the current Investigator's Brochure

7.3 Reporting Requirements for Adverse Events

Adverse events, serious adverse events, deviations, violations, and unanticipated problems must be entered into the clinical trial management system (CTMS), OnCore, and must also be reported to the following entities according to the timelines mentioned in the chart below. Serious adverse events collection will start at the time patient signs consent until 30 days after the end of treatment. Adverse events will be collected from the time the research patient begins treatment until 30 days after the end of treatment. All adverse events/serious adverse events should be followed until resolution or stabilization.

Event Type	Coordinating Center/Medical Monitor	UCI IRB	Eli Lilly Pharmaceuticals*	CFCCC DSMB
Unanticipated Problem (UP)	Within 24 hours from date the site is aware of the event, the site should enter this information into OnCore. An email notification should also be sent via email to rparajul@hs.uci.edu and uci1879@hs.uci.edu.	Within 5 business days submit an Unanticipated Problem Report (UP). Current policy can be found here.	Within 15 business days of learning of the event. Submit an SAE Form to Eli Lilly's IIR Portal for Trial Management (https://www.lillyinvestigatorresearch.com)OR via fax (866-644-1697). Serious adverse events should be reported to Lilly using a CIOMS Form or other form acceptable to Lilly.	Within 5 days from date PI is aware of the event. This information must be reported into OnCore.
AEs and SAEs (non-Unanticipated Problem)	Please refer to section 7.4 for reporting timeframes on AEs and SAEs.	N/A	Only SAEs are required to be reported within 15 business days of learning of the event. Please see section 7.6 below for additional reporting for SAEs that are non-UPs.	Please refer to section 7.4 for clarification on reporting timeframes for AEs and SAEs.
Non-compliance	N/A	N/A	N/A	Please refer to section 7.4 for reportable deviations/violations.

Serious or continuing non-compliance	Within 24 hours via email to rparajul@hs.uci.edu and uci1879@hs.uci.edu	Within 5 business days submit a New Information Report	N/A	Within 5 days from date PI is aware of the event.
Prospective/Planned Deviations	At least 5 business days prior to the event via email to rparajul@hs.uci.edu and uci1879@hs.uci.edu for approval.	At least 48 hours prior to date the request is needed by. Submit a Prospective Deviation Request form	N/A	At the time of progress review as aggregate reports.
*Patients who become pregnant must be reported along same timelines as SAE. Please reference section 7.5 below in regards to additional safety information required to be reported to Eli Lilly Pharmaceuticals for subjects who become pregnant.				

7.4 Additional Reporting Requirements to CFCCC DSMB

Site must report AE, SAE, deviations, violations, and unanticipated problems according to their institutional policies.
Institutions must also report AE, SAE, deviations, violations, and unanticipated problems to the DMSB in the following timeframes:

Adverse Events/Serious Adverse Events

Event Type	**Reporting Timeframe to CFCCC DMSB (Notification is done by entering this information into OnCore within the timelines below)**
Serious Adverse Events (all attributions) that meet all of the following criteria: ▪ Unexpected ▪ Grades 3-5	5 business days from date the PI is aware of the event

▪ Occurring during treatment or within 30 days of the end of treatment*	
Adverse Events that meet all of the following criteria: ▪ Unexpected ▪ Study related (possibly, probably, or definitely) ▪ Grades 3-4 ▪ Occurring during treatment or within 30 days of the end of treatment*	5 business days from date the PI is aware of the event
All other Adverse Events and Serious Adverse Events should be reported as noted in the 'Recording of Events' section	Prior to each scheduled progress review.
** Investigators are not obligated to actively seek information regarding the occurrence of new AEs or SAEs beginning after the 30-day post-treatment period. However, if the investigator learns of such an event and that event is deemed relevant to the study, he/she should promptly document and report the event.*	

Deviations and Violations

Event Type	Reporting Timeframe to CFCCC DSMB (Notification is done by entering this information into OnCore within the timelines below)
Violations as defined above (e.g. wrong dosage of drug administered, safety procedures not being conducted at specific time points).	5 business days from the date the PI is aware of the event
Deviations as defined above, including: ▪ Planned deviations (e.g. rescheduling a visit that will be out of window due to a holiday) ▪ Unplanned deviations (e.g. rescheduled visit, a missed routine safety laboratory test for a participant with previously normal values)	Prior to each scheduled progress review

7.5 Additional Clinical Reporting Requirements to Eli Lilly Pharmaceuticals

Eli Lilly Pharmaceuticals requires that all SAEs related to study drug are reported via Eli Lilly's IIR Portal for Trial Management (https://www.lillyinvestigatorresearch.com) OR via fax (866-644-1697). Serious adverse events should be reported to Lilly using a CIOMS Form or other form acceptable to Lilly. Eli Lilly Pharmaceuticals does not require the report of other events of special interest.

7.6 Other Non-Clinical Reporting Guidelines to Eli Lilly Pharmaceuticals

Other information such as milestone dates, milestone dates met, enrollment updates, protocol amendments, site information, and expenses (invoices) can be updated in Eli Lilly's IIR Portal for Trial Management (https://www.lillyinvestigatorresearch.com) by the study members assigned by the principal investigator.

8.0 DRUG INFORMATION

8.1 Abemaciclib

A list of the adverse events and potential risks associated with Abemaciclib can be found in the investigator brochure available in OnCore

- Other names for the drug(s): Verzenio
- Classification - type of agent: Antineoplastic
- Mode of action: Cyclin-dependent kinase inhibitor
- Storage and stability: Store at room temperature, refer to product label for specific storage range and instructions."
- Protocol dose: 150 mg BID, Abemaciclib will be provided in 50mg tablets only
- Preparation: N/A
- Route of administration for this study: Oral
- Availability: Provided by Eli Lilly
- Side effects: Common side effects are Diarrhea, Neutropenia, Nausea, abdominal pain, fatigue, anemia, leucopenia, vomiting, thrombocytopenia, thromboembolism

8.2 Fulvestrant

A list of the adverse events and potential risks associated with Fulvestrant are found in package insert.

- Other names for the drug(s): Faslodex

- Classification - type of agent: Antineoplastic
- Mode of action: Estrogen receptor antagonist
- Storage and stability: Refrigerate, 2 to -8°C, protect from light, store in original cartoon until time of use
- Protocol dose: Supplied at 50mg/ml. Protocol dose 500 mg.
- Preparation: Solution
- Route of administration for this study: Intramuscular
- Availability: Commercially available
- Incompatibility: There are no known drug-drug interactions. Fulvestrant does not significantly inhibit any of the major CYP isoenzymes, and studies of co-administration of fulvestrant with midazolam indicate that therapeutic doses of fulvestrant have no inhibitory effects on CYP3A4 or alter blood levels of drug metabolized by that enzyme. Also, although fulvestrant is partly metabolized by CYP3A4, a clinical study with rifampin, an inducer of CYP3A4, showed no effect on the pharmacokinetics of fulvestrant. Clinical studies of the effect of strong CYP3A4 inhibitors on the pharmacokinetics of fulvestrant have not been performed.
- Handling: Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage. NIOSH recommends double gloving, a protective gown, ventilated engineering controls (a class II biological safety cabinet or a compounding aseptic containment isolator), and closed system transfer devices (CSTDs) for preparation. Double gloving and a protective gown are recommended during administration (NIOSH 2016).
- Side effects: Fatigue, Headache, Hot flash, Anemia, Nausea, cough, increase in creatinine, peripheral edema, dizziness, pruritus, skin rash, back pain, anorexia, hypersensitivity reactions, and thromboembolism. Increase hepatic enzymes also can occur.

  Hot flashes (23.5%) are the most commonly reported adverse reaction to fulvestrant during second line hormonal therapy for breast cancer. Vaginal irritation (3.4%) has also been reported with fulvestrant.

  UTI adverse reactions occurred in up to 9.3% of patients receiving fulvestrant.

  Joint disorders have been reported in 9.3% of patients.

  Others include nausea, vomiting, constipation, diarrhea and abdominal pain, headache, back pain, and pharyngitis.

Thromboembolism has been reported in patients treated with fulvestrant (3.5%). The incidence of thrombosis is less than that reported with tamoxifen (6.5%) or megestrol (4.7%) during clinical trials.

Injection site reactions with mild transient pain and inflammation occurred in 7% of patients (1% of treatments) given the single 5ml injection of fulvestrant and withdrawal secondary to that was 2.5%.

Other adverse events reported as drug-related and seen infrequently (< 1%) include thromboembolic phenomena, myalgia, vertigo, and leukopenia.

Vaginal bleeding has been reported infrequently (< 1%), mainly in patients during the first 6 weeks after changing from existing hormonal therapy to treatment with fulvestrant. If bleeding persists, further evaluation should be considered.

- Contraindications: Hypersensitivity reaction

- Warning and precaution:
  -Blood disorders: Should be used with caution in patients with bleeding diathesis, thrombocytopenia or anticoagulant use
  -Hepatic Impairment: A 250mg dose is recommended in patients with moderate hepatic impairment
  -Pregnancy: Women should be advised of potential hazard to the fetus and to avoid becoming pregnant while receiving Faslodex

8.3 Agent Accountability

Accountability for the study drug at the study center is the responsibility of the Investigator. The Investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign drug accountability responsibilities to a pharmacist or other appropriate individual.

The Investigator or delegate will maintain accurate drug accountability records indicating the drug's delivery date to the site, inventory at the study center, use by each patient, and destruction.

These records will adequately document that the patients were provided the doses as specified in the protocol and should reconcile all study drug received from Eli Lilly Pharmaceuticals.

Study drug must not be used for any purpose other than the present study. Study drug that has been dispensed to a patient and returned unused must not be redispensed to a different patient.

Patients will receive instructions for home administration of Abemaciclib according to the regimen description above. Abemaciclib is to be taken twice a day. If doses of Abemaciclib are missed or held, the patient should not make up for the missed doses. Patients will be given a study medication diary to complete at home for Abemaciclib. Compliance with the dosing regimen will be assessed based on completion of the drug diary and return of unused drug (or empty bottles).

IMP Destruction
IMP will be destroyed by the sites according to their institutional policies. Documentation of IMP destruction should be made available to Eli Lilly Pharmaceuticals at the end of the study.

IMP Returns

Eli Lilly Pharmaceuticals will not accept returned IMP

9.0 CORRELATIVE STUDY

Molecular analysis in the form of Next Generation Sequencing (NGS) will be performed on the treatment naïve archival breast tissue, on the breast tissue at the time of recurrence and on the surgical specimen. Blood will be collected as well for analysis of ctDNA before enrollment, every 3 months while on the treatment and then every 6 months (after definitive surgery) until the end of the study at five years. The molecular analysis by NGS will be done by Tempus using their standard platform.

Correlative Study Objective:

1. To determine if genomic analysis of patient matched breast tissue samples and serial mutational tracking of ctDNA can identify new mechanisms of endocrine resistance and the way Abemaciclib overcomes endocrine resistance
2. To determine the mechanism of response or resistance to Abemaciclib
3. To determine biomarkers related to the Rb pathway

Collection of tumor samples (archival, at time of recurrence, and from surgery) and ctDNA blood are mandatory.

10.0 STATISTICAL CONSIDERATIONS

Pathological response (pCR) is a tool to measure the efficacy of Neo-Adjuvant therapy. A complete pCR is defined as the absence of invasive cancer in the tumor and/or the axillary lymph node in the surgical pathology specimen after undergoing Neo-Adjuvant therapy. Chemotherapy can shrink HR- positive tumors and facilitate better surgical options, but is less likely to achieve a pathologic complete response (pCR) in HR-positive cancers, especially luminal A cancers, than for more proliferative histologies. Multiple metaanalysis have shown that pCR has prognostic implications even in patients with HR+ breast cancer. However, a limitation of using pCR to predict outcomes in patients with ER+ disease is that only 2 to 10 percent of patients with ER + disease achieve a pCR with NACT. In the post-menopausal setting, Aromatase Inhibitors are recommended over Tamoxifen as Neoadjuvant endocrine therapy based on clinical trials and meta-analysis. AIs resulted in higher clinical response rate (OR 1.69, 95% CI 1.36-2.10), radiologic response rate (OR 1.49, 95% CI 1.18-1.89), and BCS rate (OR 1.62, 95% CI 1.24-2.12) compared with tamoxifen (18).

Several trials have also investigated the role of endocrine therapy in combination with other targeted therapies. For example, in the randomized phase II UNICANCER-NEOPAL study, the combination of neoadjuvant palbociclib and letrozole resulted in slightly lower pCR rates compared with neoadjuvant third-generation chemotherapy, but the rates of clinical response and breast-conserving surgery were similar, with less frequent serious adverse events (19).
Another study compared different doses of neoadjuvant fulvestrant (500 mg/month versus 250 mg/month) given for 16 weeks prior to surgery (20). Similar to what has been observed in the metastatic setting, the study demonstrated that the higher dose of fulvestrant was superior and had a greater antiproliferative effect. At week 16, tumor response rates were 22.9 and 20.6% for fulvestrant 500 and 250 mg, respectively, with considerable decline in all markers by both imaging and the ER/PR scoring method.

Several ongoing trials are investigating the role of combination therapy, including the combination of AIs with cyclin-dependent kinase (CDK) 4/6 inhibitors (NeoMONARCH), PI3K inhibitors (LORELEI), and dual endocrine therapy (ALTERNATE).

The NeoMONARCH study randomly assigned postmenopausal women with early stage HR+ breast cancer to Neoadjuvant therapy with Anastrozole, Abemaciclib or Anastrozole with Abemacilib. The study met its primary endpoint by showing that Ki67 levels were significantly reduced in breast cancer cells from the 107 patients who received abemaciclib, either alone or in combination with anastrozole, compared with the 54 patients who received anastrozole only. Treatment with abemaciclib plus anastrozole led to a reduction in tumor size in most patients, as assessed by clinical and radiologic evaluation. Patients in this study received Abemaciclib only for two weeks. Therefore, extending Neo- Adjuvant Abemaciclib (beyond two weeks) as proposed in the current trial and combining it with high dose Fulvestrant is expected to achieve a higher response rate, greater anti-proliferative effect as measured by the Ki-67 index and perhaps improve Breast conservation surgery (21).
Similarly, the MONARCH 2 study compared the efficacy and safety of abemaciclib plus fulvestrant with fulvestrant alone in patients with advanced HR + breast cancer. Abemaciclib plus fulvestrant significantly extended PFS versus fulvestrant alone (median, 16.4 v 9.3 months; hazard ratio, 0.553; 95% CI, 0.449 to 0.681; P < .001). In patients with measurable disease, abemaciclib plus fulvestrant achieved an ORR of 48.1% (95% CI, 42.6% to 53.6%) compared with 21.3% (95% CI, 15.1% to
27.6 %) in the control arm (22).

The MONALEESA-3 study was a phase III study evaluated ribociclib plus fulvestrant in patients with hormone receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer who were treatment naïve or had received up to one line of prior endocrine therapy in the advanced setting. Among patients with measurable disease, the overall response rate was 40.9% for the ribociclib plus fulvestrant arm and 28.7% for placebo plus fulvestrant (23).
The cohort in the proposed trial have had local recurrence while on adjuvant endocrine therapy. Hence, they are expected to have molecular evidence of endocrine resistance. Since Fulvestrant and CDK 4/6 inhibition have been shown to benefit patient with endocrine resistance, we expect that Neo-Adjuvant Abemaciclib with Fulvestrant with achieve a response rate, greater antiproliferative effect as measured by the Ki-67 index and perhaps improve Breast conservation surgery too.

10.1 Study Design

This study is a prospective, open-label, single-centered, phase II trial.

10.2 Sample Size and Accrual and Data Analyses Plans

Tumor Registry data at UCIMC shows that we have had 960 patients with Hormone Receptor positive breast cancer from 2012-2017. The 2018 data is currently not populated by the tumor registry. Similarly, from 1/1/14 to 6/14/2019, there have been 456 patients accrued in breast cancer trials out of which, 155 patients were enrolled in treatment trials. In order to obtain 30 evaluable breast cancer participants to examine the primary hypothesis, we will need to screen 680 invasive breast cancer patients (this is clearly possible due to the cohort of 960 patients from 2012-2017). Based on the data from California Cancer Registry and estimated percentage of recurrence, we estimate that approximately around 10% of 680 invasive breast cancer patients are post-menopausal, have histologically been confirmed with HR+, have localized non-metastatic breast cancer and will have recurrence. Of the 68 patients, we estimate that there are 59 (87% of 68) patients who are also on adjuvant endocrine therapy. The mutation ESR1 is

detected in 11-54% of patients with advanced breast cancer especially during the progression of hormonal therapy. Therefore, we estimate that there are 32 (54% of 59) patients who have ESR1 gene mutation/any known molecular evidence of endocrine resistance. To take into account of 5% attribution, we will need to enroll 32 subjects to receive the study treatment to ensure that there are 30 evaluable breast cancer participants. The plan of enrollment is over a four-year period. Hence, with the adequate number of patients justified from UCIMC tumor registry data and extending the period of enrollment from to four years, enrolling the sample size of 30 patients over a period of four years is feasible.

Table x1:Power and sample sizes of Simon's two-stage design

N	n_1	r_1	r_2	Type 1 Error	Power	EN_0	Probability of early stopping	p_0	p1
29	10	1	5	0.0471	0.8051	15	0.7361	0.1	0.3

Table X1 presents sample size of Simon's two-stage design. Where n is the total number of subjects, n1 is the number of subjects accrued during stage 1, if r1 or fewer responses are observed during stage 1, the trial is stopped early for futility. If r2 or fewer responses are observed by the end of stage two, then no further investigation of the drug is warranted, EN0 is the expected sample size for the trial when response rate is p0 and p0 and p1 are the response probabilities under the null and under the alternative hypothesis. Thus, the null hypothesis that the true response rate is 10% will be tested against a one-sided alternative. In the first stage, 10 patients will be accrued. If there are one or fewer responses in these 10 patients, the study will be stopped. Otherwise, 19 additional patients will be accrued for 29. The null hypothesis will be rejected if 6 or more responses are observed in 29 patients. This design will yield a type I error rate of 0.0471 and power of 80% when the true response rate is 0.3. Thus, we anticipate recruiting 29 evaluable participants with at least 10 in stage 1. (Simon 1984, Jung et al 2004) (16, 17).Given the sample size of 30 participants, power in the statistical design will be low for the secondary and exploratory endpoints. Efficacy of the study as measured by estimating the objective response rate in the breast and/or the axillary lymph nodes or determining if the combination of Abemaciclib and Fulvestrant increases the percentage of patients who undergo breast conserving surgery will be measured by constructing 95% CI. We plan to use survival analysis methods such as Kaplan- Meier estimates of survival probability for univariate analysis and log rank tests in order to test for differences among different patient characteristics such age group for recurrence or disease-free survival. For multivariate analysis in order to examine survival adjusted for a number of covariates we plan to use the Cox proportional hazards model.In order to examine the safety and toxicity which will be determined by the incidence of treatment-emergent, treatment-related adverse events (TRAEs), and serious adverse events (SAE) we plan to monitor side effects and adherence to the protocol throughout the duration of the study. Interim analyses will be performed to assess the presence of side effects. Contingency tables will be constructed to compare the proportion of patients with side effects by study characteristics as age, race ethnicity and other clinical and epidemiologic characteristics. Distributions of all data items will be generated and examined for the presence of outliers, in order to assess the general form of the distributions, and to compute measures of central tendency and variability. Trellis graphics will be used for data display including histograms, boxplots, and Q-Q normal plots. In addition, we plan to examine if genomic analysis of patient matched breast tissue samples and serial mutational tracking of circulating tumor DNA can identify new mechanisms of endocrine resistance and how

Abemaciclib overcomes endocrine resistance. For the analyses with matched pair tissue data we will use paired t tests or Wilcoxon sign rank statistical analysis in order to test differences in recurrent and treated breast tissue. We plan to measure absolute values and changes in circulating tumor DNA and correlate them with endocrine resistance. If serial monitoring of ctDNA can provide markers of resistance, we will quantify endocrine resistance as a composite outcome that will be quantified as dichotomous variable if it happens (yes or no) and at what time interval during our study. We will start our analysis by using frequency table analysis in order to examine the relationship between resistance or sensitivity and specific mutations.

11.0 STUDY MANAGEMENT

11.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by their own institution's COI committee. All investigators will follow the University conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.2 Data Completion

11.2.1 OnCore Data Entry

Data, as indicated by Sponsor, will be entered into OnCore – UC Irvine's Clinical Trial Management system. The Investigator is responsible for ensuring all entries are accurate and correct. The Investigator must maintain accurate source data that support OnCore data entry. All data will be entered as per Sponsor's specification and timeframe.

11.2.2 Recording of Events

All investigator initiated treatment trials require that adverse events, serious adverse events, deviations, and unanticipated problems be entered into the clinical trial management system (CTMS), OnCore. All entries must be entered in OnCore within the timelines specified in section 7.4-7.6 of being aware of the adverse event, serious adverse event, violation, deviation, or unanticipated problem. Adverse events and violations/deviations and adverse events that are unanticipated problems that require prompt reporting to the DSMB must be entered into OnCore according to the timelines as specified in section 7.3-7.5

11.3 Data and Safety Monitoring/Auditing

11.3.1 Quality Assurance

Quality assurance activities will be conducted as per UC Irvine Chao Family Comprehensive Cancer Center's Quality Assurance Monitoring and Auditing Plan and at the discretion of the CFCCC Data and Safety Monitoring Board in order to ensure patient safety and data integrity oversight. By conducting internal monitoring and auditing, the CFCCC will ensure compliance with high quality standards and all applicable regulations, guidelines, and institutional policies. Trial monitoring and auditing may be completed remotely or on-site by the Quality Assurance Officer. Participating sites may follow their own internal quality assurance policies in order to maintain patient safety and data integrity oversight. The investigator must permit study-related monitoring/auditing and provide access to study-related materials.

11.3.2 Data and Safety Monitoring Plan

This is a risk level 2 study, as defined in the Chao Family Comprehensive Cancer Center (CFCCC) Data and Safety Monitoring Plan (DSMP) because it is a study in which the IND is exempt by the FDA.

The Principal Investigator (PI), co-investigator, clinical research coordinator, and statistician are responsible for monitoring of data and safety for this study. For studies that have stopping rules for safety and efficacy, the PI will be responsible for the implementation and make changes as applicable. The CFCCC Data and Safety Monitoring Board (DSMB) is an independent body responsible for the safety of study subjects as well as the data integrity of the protocol. Data and safety will be reported to the DSMB with submission of progress reports that include aggregated reports of adverse events, serious adverse events, deviations, and violations. In addition, all adverse events, deviations, and violations will be reported promptly to the DSMB for review according to section 7.4 and section 7.5.

11.4 Protocol Deviation

All protocol deviations will be reported in accordance with UCI IRB, UCI CFCCC Stern Center policies and the participating site's IRB policies.

11.5 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

11.6 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.7 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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13.0 APPENDICES

APPENDIX A: ECOG Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.

5	Dead.	0	Dead.

APPENDIX B: Liver Safety: Suggested Actions and Follow-up Assessments

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the principal investigator.

Hepatic Monitoring Tests

Hepatic Hematology
Hemoglobin (HGB)
Hematocrit (HCT)
Erythrocytes (RBC)
Leukocytes (WBC)
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils
Platelets (PLT)

Hepatic Chemistry
Total bilirubin
Direct bilirubin
Alkaline phosphatase
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Gamma-glutamyl transferase (GGT)
Creatine phosphokinase (CPK)

Haptoglobin

Hepatic Coagulation
Prothrombin Time (PT)
Prothrombin Time, INR

Hepatic Serologies
Hepatitis A antibody, total
Hepatitis A antibody, IgM
Hepatitis B surface antigen
Hepatitis B surface antibody
Hepatitis B Core antibody
Hepatitis C antibody
Hepatitis E antibody, IgG
Hepatitis E antibody, IgM

Recommended Autoimmune Serology
Anti-nuclear antibody
Anti-smooth muscle antibody
Anti-actin antibody

APPENDIX C: Inducers and Strong Inhibitors of CYP3A

The information in this appendix is provided for guidance to investigators and does not preclude the use of these medications if clinically indeicated

Strong Inducers of CYP3A	
Carbamazepine	Rifapentine
Dexamethasone	Rifabutin
Phenobarbital/phenobarbitone	Rifampin
Phenytoin	St. John's Wort
Moderate Inducers of CYP3A	
Bosentan	Primidone
Lenisurad	Telostristat ethyl
Modafinil	
Strong Inhibitors of CYP3A	
Aprepitant	Itraconazole

Ciprofloxacin	Ketoconazole
Clarithromycin	Nefazodone
Conivaptan	Posaconazole
Diltiazem	Troleandomycin
Erythromycin	Verapamil
Fluconazole	

APPENDIX D: Pill Diaries

Pill Diary Cycle 1

UCI 18-79 Abemaciclib Pill Diary	**Cycle: 1**
Subject Initials: ___ ___ ____ Subject ID: _____ Current Total Dosage: _____	
Dosing Instructions: Abemaciclib will be taken twice a day, once in the morning and once in the evening. If you forget to take a dose, do not make up the dose and record that the dose was skipped. Please record the date and times you take the Abemaciclib. Please remember to bring your bottles and Pill Diary to each clinic visit. If you experience any symptoms, please do not take the dose and contact the Study Team. Treating Investigator: _____ Nurse Navigator: _____ Next Clinic Visit: _____ Study Coordinator: _____	

Day 1 (Same day as 500mg Fulvestrant Injection)		Date: _____
Dose taken in the morning:	_____ mg	Time of morning dose: _____
Dose taken in the evening:	_____mg	Time of morning dose: _____
Comments:		
Day 2		Date: _____
Dose taken in the morning:	_____ mg	Time of morning dose: _____
Dose taken in the evening:	_____mg	Time of evening dose: _____
Comments:		
Day 3		Date: _____
Dose taken in the morning:	_____ mg	Time of morning dose: _____
Dose taken in the evening:	_____mg	Time of evening dose: _____
Comments:		
Day 4		Date: _____

Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 5		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 6		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 7		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 8		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 9		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 10		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 11		Date: _____

Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 12		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 13		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 14		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 15 (same day as 500mg Fulvestrant injection)		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 16		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 17		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 18		Date: _____

Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 19		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 20		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 21		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 22		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		

Pill Diary Cycle 2 and Forward

UCI 18-79 Abemaciclib Pill Diary	**Cycle: _____**
Subject Initials: ___ ___ ____ Subject ID: _____	Current Total Dosage: _____

Dosing Instructions:
Abemaciclib will be taken twice a day, once in the morning and once in the evening.
If you forget to take a dose, do not make up the dose and record that the dose was skipped.
Please record the date and times you take the Abemaciclib.
Please remember to bring your bottles and Pill Diary to each clinic visit.
If you experience any symptoms, please do not take the dose and contact the Study Team.

Treating Investigator: _____
Nurse Navigator: _____ Next Clinic Visit: _____
Study Coordinator: _____

Day 1 (Same day as 500mg Fulvestrant Injection)		Date: _____
Dose taken in the morning:	_____ mg	Time of morning dose: _____
Dose taken in the evening:	_____mg	Time of morning dose: _____
Comments:		
Day 2		Date: _____
Dose taken in the morning:	_____ mg	Time of morning dose: _____
Dose taken in the evening:	_____mg	Time of evening dose: _____
Comments:		
Day 3		Date: _____
Dose taken in the morning:	_____ mg	Time of morning dose: _____
Dose taken in the evening:	_____mg	Time of evening dose: _____
Comments:		
Day 4		Date: _____
Dose taken in the morning:	_____ mg	Time of morning dose: _____
Dose taken in the evening:	_____mg	Time of evening dose: _____
Comments:		
Day 5		Date: _____
Dose taken in the morning:	_____ mg	Time of morning dose: _____
Dose taken in the evening:	_____mg	Time of evening dose: _____

Comments:		
Day 6		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 7		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 8		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 9		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 10		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 11		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 12		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		

Day 13		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 14		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 15		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 16		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 17		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 18		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 19		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 20		Date: _____

Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 21		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		
Day 22		Date: _____
Dose taken in the morning: Dose taken in the evening:	_____ mg _____mg	Time of morning dose: _____ Time of evening dose: _____
Comments:		

APPENDIX E: Definitions

Inflammatory Disease: Erythema AND peau d'orange involving 1/3 or more of the breast with a histological diagnosis of breast cancer. The finding of focal dermal lymphatic involvement on histology does not constitute inflammatory breast cancer.

PEPI Score: The PEPI Score (preoperative endocrine prognostic index) is a score that is used in clinical trials to assess response to Neo-Adjuvant endocrine therapy. The PEPI score takes into account the tumor and nodal stage, level of ER expression and Ki 67 following neoadjuvant endocrine therapy.

UNIVERSITY OF CALIFORNIA, IRVINE
CONSENT TO ACT AS A HUMAN RESEARCH SUBJECT

UCI 18-79: A Phase II Open Label Trial of Neo-Adjuvant Abemaciclib with Fulvestrant in Patients Who Develop Localized Recurrence While on Adjuvant Endocrine Therapy with Molecular Evidence of Endocrine Resistance
(MP 09/09/20, Main ICF v4 09/09/2020)

Lead Researcher
Ritesh Parajuli, HS Assistant Clinical Professor
Department of Medicine
(714) 456-5153; rparajul@uci.edu
24-Hour Telephone Number/Pager: (714) 506-2420

Other Researchers
Rita Mehta, MD
Kari Kansal, MD
Karen Lane, MD
Erin Lin, MD
Paul Coluzzi, MD
Andreea Nanci, MD
Rupali Nabar, MD
Khosrow Mahdavi, MD

STUDY LOCATION(S):
UC Irvine Health
Chao Family Comprehensive Cancer Center
101 The City Drive South, Building 23
Orange, CA 92868

UC Irvine Health – Newport Cancer Center
1640 Newport Blvd
Costa Mesa, CA 92627

STUDY SPONSOR(S):
UCI

SUMMARY OF KEY INFORMATION:

The information provided in this box includes a brief yet complete summary of key information about the research, presented first as required by the federal regulations. Some sections that require additional information may be repeated later in this document.

Participation is Voluntary
You are being asked to participate in a research study. Participation is completely voluntary. Please read the information below and ask questions about anything that you do not understand. A researcher listed above will be available to answer your questions.

Study Purpose
The purpose of this research study is to determine if the combination of abemaciclib plus fulvestrant before surgery will destroy as much cancer as possible that will allow a complete pathologic response

to be achieved. A Complete pathologic response is defined as the absence of breast cancer in the breast and/or the axillary (a person's armpit) lymph nodes in the surgical specimen.

You should also have demonstrated evidence of resistance to endocrine therapy by next generation sequencing of the breast tissue. Next generation sequencing is a test that looks for mutations in your genes.

Study Procedures

This study will consist of a screening period of up to 28 days. After screening procedures have been completed, the investigator will evaluate the results and your medical history to see if you are eligible for the trial. If you are eligible, you will take abemaciclib twice daily by mouth in combination with fulvestrant. Fulvestrant will be injected into your muscle . Abemacilib and Fulvestrant will be administered for as long you tolerate the treatment, achieve maximum response per investigator's assessment, or until your cancer gets worse. If your cancer comes back again during the course of treatment, a fresh biopsy will be obtained if clinically feasible. Prior to surgery and within 30 days of your last dose of treatment, you will be evaluated by your treating investigator for safety assessments, which will include physical exam, laboratory tests, and review of any new or ongoing symptoms. After the last treatment with Abemaciclib and Fulvestrant, you will undergo surgery as the standard of care. The surgical pathology will be examined to see if there is any residual cancer or not.

This study also includes additional research studies, often called a correlative study, where extra blood will be collected to test for ctDNA (circulating tumor DNA), which are fragmented DNA that travel the bloodstream. This test is to have a better understanding on how or why some tumor cells is not affected by hormone therapy (endocrine resistance), how abemaciclib overcomes endocrine resistance as well as the mechanism of response or resistance to abemaciclib and to identify other relevant biomarkers (genes that may be an endocrine resistance indicator). The ctDNA collection will occur at screening, every 3 months while on treatment and every 6 months (after definitive surgery) until the end of the study at 5 years. In addition to the collection of your blood, the correlative study will also be looking at your collected tissue at screening, during your regularly scheduled surgery and tissue that is collected if your cancer has gotten worse. Next generation sequencing (NGS) testing will be done on these tissue samples.

Expected Duration

Participation will be every two weeks for clinic visits and treatment for the first cycle and every four weeks for subsequent cycles as long as you are in the study. Each cycle is 28 days. There will be MRI imaging of your breast every 12 weeks from your first dose of therapy during the treatment phase. The duration of treatment and the duration of visit to your treating physician can vary anywhere from two to four hours. You will remain on study as long as you show a best response per treating investigator's clinical judgement, the disease is controlled and you are able to tolerate treatment. Response to the treatment will be made by the treating physician by clinical assessment and comparing the size of the tumor before and after treatment. Best response will be defined as the smallest reduction in the size of the tumor prior to surgery. After you come off treatment, you will have surgery, and after surgery, you will be followed for ctDNA blood collection every 6 months for up to 5 years.

Risks of Participation

The more notable risks of participation include side effects associated with the study drugs including fatigue, nausea/vomiting, low blood count with increased risk of infection or bleeding. Should there be a breach in confidentiality of your data, there is a slight risk that your private medical information could be shared with individuals who are not members of the study team.

Benefits to Participants

Taking part in this study may or may not make your health better. While researchers hope the combination of abemaciclib and fulvestrant controls the disease longer than the standard (usual) treatment, there is no proof of this yet.

Benefits to Others or Society
This study will help researchers learn more about the combination of abemaciclib and fulvestrant and it is hoped that this information will help in the treatment of future patients with breast cancer.

Alternative Procedures or Treatments
If you decide not to participate, or if you withdraw from this study before it is completed, your other choices may include:

- Getting no treatment
- Getting standard treatment for your condition without being in a study such as surgery, or treatments such as Fulvestrant and CDK4/6 inhibitors, drugs that restore a protein which prevents cancer cells from growing
- Getting a different experimental treatment/taking part in another study.

WHY IS THIS RESEARCH STUDY BEING DONE?

The main reason for you to take part in this study is that by treating you, the following research question could be answered:

Does the combination of abemaciclib plus fulvestrant improve a pathologic complete response (a complete response is defined as the absence of breast cancer in the breast and/or the axillary (a person's armpit) lymph nodes in the surgical specimen) in Hormone Receptor positive patients whose breast cancer came back in the breast and not spread to other distant organs (localized non-metastatic breast cancer) and demonstrate molecular resistance to endocrine therapy after being treated with adjuvant hormone therapy.

"Investigational/Experimental" means that the drugs (abemaciclib plus fulvestrant) being tested have not been approved for the use described in this study by the United States Food and Drug Administration (FDA). Both of the study drugs, abemaciclib and fulvestrant, are FDA approved drugs for indications other than as being used in this study. Both Abemaciclib and Fulvestrant are approved for patients with mestastic (cancer that has spread from the site of origin to other parts of the body) breast cancer whose cancer has worsened.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Approximately 32 participants will take part in the research at UCI.

AM I ELIGIBLE TO PARTICIPATE IN THIS STUDY?

Please note this may not be a complete list of eligibility criteria. We have included a few examples of study criteria to help you better understand how your eligibility in the study will be determined; your study team will go through the study eligibility criteria with you to verify if you qualify for participation in this study.

Inclusion Requirements
You can participate in this study if you

- Are at least 18 years of age or older
- Must have Stage I, Stage II and stage III breast cancer
- Must be post-menopausal
- Able to swallow oral medications
- Must be able to sign a written informed consent, are reliable, willing to be available for the duration of the study and are willing to follow study procedures

Exclusion Requirements
You cannot participate in this study if you

- Have Stage IV metastatic breast cancer

- Are premenopausal
- Have HER2 negative or triple negative breast cancer
- Prior treatment with either abemaciclib (or similar compound) and/or fulvestrant
- Have a history of any other cancer (except for non-melanoma skin cancer or carcinoma in situ of the cervix) that has not been in remission for the past three years or have not received a stem-cell transplant

HOW LONG WILL THE STUDY GO ON?

This study will consist of a screening period of up to 28 days. You will take abemaciclib twice daily by mouth in combination with Fulvestrant, which will be injected into your muscle for as long you respond to treatment, can tolerate the treatment or until your cancer gets worse. After treatment is complete, you will have surgery as standard of care. After your surgery, you will be followed every 6 months for ctDNA blood collection for up to 5 years.

WHAT PROCEDURES ARE INVOLVED WITH THIS STUDY?

Before you can participate in the main part of the study...

You will need to have "screening" exams, tests or procedures. The screening process helps the researchers decide if you meet the study requirements listed below and must be done within 28 days before starting treatment. The screening procedures include:

- We will review your medical history, including your cancer history
- We will do a physical examination. It will also include a recording of your height and weight.
- We will collect blood for safety tests. This is done as part of your regular cancer care.
- We will collect blood for ctDNA analysis. ctDNA is portion of your DNA from your tumor that is circulating in your bloodstream. The amount of blood collected will be about 17 ml (approximately 3.5 teaspoons).
- We will review any medications that you take, including over-the-counter drugs vitamins, and herbal products.
- We will ask how you are feeling and if your level of activity has changed.
- We will look at places where your tumors can come back. We will use one of the tests described below. Your study doctor will decide what test is best for you. This is being done as part of your regular cancer care. These images will include your chest, abdomen and pelvis.
    - Computed Tomography (CT) Scan: This test uses a small amount of radiation (x-ray) to take pictures of the inside of your body. It can show a cross section, like a thin "slice" of your body, or it can show the body tissues and structures in "3-D". For this test, the study doctor or staff may give you a contrast dye, either by mouth or injected into a vein with a needle. The study doctor or staff can tell you more about the contrast dye.
    - Magnetic Resonance Imaging (MRI) Scan: This test uses powerful magnets and radio waves to make pictures of body tissues and structures. During an MRI, you must lie on your back in the MRI scanner without moving. The inside of the MRI scanner is a tight space. You may have a contrast dye given by mouth or injected into a vein with a needle. The study doctor or staff can tell you more about the contrast dye.
- After you provide your consent to participate in this study, your study doctor will arrange for a sample of your cancer to be evaluated for molecular testing. This can be taken from tissue that was obtained from a previous biopsy/surgery or it can be a new biopsy. This tissue will be utilized for the correlative portion of the trial.

During the main part of the study...

If the screening exams, tests and/or procedures show that you can continue to be in the study, and you choose to take part, then you will have the following procedures and tests done. You will take abemaciclib twice daily by mouth in combination with Fulvestrant that will be injected into your muscle for as long you tolerate the treatment, a maximal response is obtained or until your cancer gets worse. After the treatment phase is over, you will have surgery as the standard of care.

The main study tests and procedures include:

- We will review your medical history, including your cancer history.
- We will do a physical examination. This also includes a recording of your weight.
- We will review any medications that you take, including over-the-counter drugs vitamins, and herbal products.
- We will collect blood for safety tests. This is being done as part of your regular cancer care.
- We will collect blood for ctDNA analysis every three months while on treatment and then every 6 months after surgery until the end of the study at five years. The amount of blood collected each time will be about 17 ml (approximately 3.5 teaspoons).
- We will ask how you are feeling and if your level of activity has changed.
    - You will have an MRI scan of your breast every 12 weeks after your first dose of treatment. MRI will be done every 12 weeks while on the treatment. The size of the tumor in the MRI prior to treatment and after treatment will determine the best response. Magnetic Resonance Imaging (MRI) Scan: This test uses powerful magnets and radio waves to make pictures of body tissues and structures. During an MRI, you must lie on your back in the MRI scanner without moving. The inside of the MRI scanner is a tight space. You may have a contrast dye given by mouth or injected into a vein with a needle. The study doctor or staff can tell you more about the contrast dye.

After you complete the main part of the study
You will undergo the following visits:

Off Treatment Visit
If you finish treatment or decide to stop taking part in the study, we will contact you to come in for a follow up visit. This will take place within 30 days after you have finished taking the study drug and prior to surgery. The procedures in this visit include:

- We will review your medical history, including your cancer history.
- We will do a physical examination. This also includes a recording of your weight.
- We will collect blood for safety tests. This is being done as part of your regular cancer care.
- We will collect blood for ctDNA analysis ctDNA is portion of your DNA from your tumor that is circulating in your bloodstream.
- We will collect a fresh biopsy if your cancer has gotten worse and if clinically feasible. Some of the tissue from this biopsy will be used for the correlative portion of the trial.
- We will ask how you are feeling and if your level of activity has changed.
- We will review any medications that you take, including over-the-counter drugs vitamins, and herbal products.

Surgery

You will undergo surgery as part of your regular care even if you were not participating in this research study. Details will be explained by your treating physician. Some of the tissue from this surgery will be used for the correlative portion of the trial.

Follow-up
After you complete surgery, we will collect blood for ctDNA every 6 months until the end of the study at 5 years.

RETURN OF RESULTS
You will not be provided any clinically relevant information that may pertain to your health.

WHAT ARE THE POSSIBLE SIDE EFFECTS OR RISKS RELATED TO THE STUDY?
You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don't know all the side effects that may happen. Side effects may be mild or very serious. The researchers may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking abemaciclib and Fulvestrant. In some cases, side effects can be serious, long lasting, or may never go away. In some cases side effects may result in death.

You should talk to the research team about any side effects you experience while taking part in the study.

Risks and side effects related to abemaciclib and Fulvestrant include those which are:

Abemaciclib

Safety information available (as of 26 September 2018) from 4299 patients with cancer and 328 healthy subjects who have taken abemaciclib has been reviewed.

Abemaciclib given alone:

Very Common (Reported in 10 or more out of 100 subjects) (greater than or equal to 10%)

- Loose stools (diarrhea)
    - The study team will discuss with you how to properly manage this side effect. You may be prescribed medicines to prevent this.
- Lack of energy (fatigue)
- Feeling sick to the stomach
- Vomiting
- Low appetite (decreased appetite)
- Decreased number of white blood cells count in the blood; this may make infections more likely to occur (neutropenia; leukopenia)
- Low red blood cell count in the blood that may make you feel more tired (anemia)
- Decreased number of platelets in the blood; this may cause bruising, difficulty with clotting of blood, or bleeding easily (thrombocytopenia)
- Dry mouth
- Inflammation or ulcers inside the mouth (stomatitis)
- Taste changes or bad taste in the mouth (dysgeusia)
- Hair loss (alopecia)

Common (Reported in 1 or more but less than 10 out of 100 subjects) (greater than or equal to 1% but less than 10%)

- Decreased number of lymphocytes in the blood; this may make infections more likely to occur (lymphopenia).
- Inflammation of the lungs causing coughing and difficulty breathing (interstitial lung disease/pneumonitis).

Very often, increases in creatinine levels, a substance in the blood that measures kidney function, were noted by laboratory testing. While abemaciclib does not decrease kidney function, creatinine increases may indicate the need for other tests of kidney function.

Other chemotherapy drugs and other forms of treatment will also have their own, often unique, side effects that should be taken into account when considering the likely effects of the treatment combination as a whole.

Abemaciclib in combination with fulvestrant was given to 441 patients. Patients treated with this combination may experience the side effects listed for abemaciclib given alone. In addition, other side effects that occurred in these patients included:

Very Common (Reported in 10 or more out of 100 subjects) (greater than or equal to 10%)

- Infections
- An increase in liver enzymes made by the liver (alanine aminotransferase increased, aspartate aminotransferase increased)
- Itching (pruritus)
- Dizziness
- Rash
- Muscle weakness

Common (Reported in 1 or more but less than 10 out of 100 subjects) (greater than or equal to 1% but less than 10%)

- Dry skin
- Increased watering of eyes (lacrimation increased)
- Blood clots in veins (venous thromboembolic events)

Fulvestrant

Like all medicines, this medicine can cause side effects, although not everybody gets them.
You may need immediate medical treatment if you experience any of the following side effects:

- Allergic (hypersensitivity) reactions, including swelling of the face, lips, tongue, and/or throat that may be signs of anaphylactic reactions
- Thromboembolism (increased risk of blood clots)
- Inflammation of the liver (hepatitis)
- Liver failure

Tell your doctor, pharmacist, or nurse if you notice any of the following side effects:

Very Common side effects (may affect more than 1 in 10 people) (greater than or equal to 10%)

- Injection site reactions, such as pain and/or inflammation
- Abnormal levels of liver enzymes (in blood tests)
- Nausea (feeling sick)
- Weakness, tiredness
- Joint and musculoskeletal pain
- Hot flushes
- Skin rash
- Allergic (hypersensitivity) reactions, including swelling of the face, lips, tongue, and/or throat

All other side effects:

Common side effects (may affect up to 1 in 10 people) (greater than or equal to 1% but less than 10%)

- Headache
- Vomiting, diarrhea, or loss of appetite

- Urinary tract infections
- Back pain
- Increase of bilirubin (bile pigment produced by the liver)
- Thromboembolism (increased risk of blood clots)
- Decreased levels of platelets (thrombocytopenia)
- Vaginal bleeding
- Lower back pain irradiating to leg on one side (sciatica)
- Sudden weakness, numbness, tingling, or loss of movement in your leg, especially on only one side of your body, sudden problems with walking or balance (peripheral neuropathy)

Uncommon side effects (may affect up to 1 in 100 people) (less than 1%)

- Thick, whitish vaginal discharge and candidiasis (infection)
- Bruising and bleeding at the site of injection
- Increase of gamma-GT, a liver enzyme seen in a blood test
- Inflammation of the liver (hepatitis)
- Liver failure
- Numbness, tingling and pain
- Anaphylactic reactions

Blood draw: Removing blood by a needle may cause temporary pain, bruising, bleeding, swelling, dizziness, and on rare instances fainting or infection.

Unknown risks: There may be risks related to the research that we do not know about yet. However, you will be informed of any additional risks to which you may be exposed, and any changes that are made to the study, as a result of any newly-identified risks.

Reproductive Risks: You should not get pregnant while in this study. Abemaciclib used in this study could harm an unborn baby. Check with the researchers about what types of birth control, or pregnancy prevention, to use while in this study.

You should also not breastfeed a baby while in this study, as the the study drug used in this study could harm a newborn baby.

If you are a male, you should not father a baby while on this study.

If you or your partner does become pregnant during the study, you should contact the researchers immediately.

WILL I BE PAID FOR TAKING PART IN THIS STUDY?

You will not be compensated for your participation in this research study.

Reimbursement

You will not be reimbursed for any out of pocket expenses, such as parking or transportation fees.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

The study supporter (Eli Lilly and Company) will supply abemaciclib tablets at no cost while you take part in the study. You and/or your health plan/insurance will need to cover the cost of the injection of Fulvestrant. Any additional research-related tests, procedures or visits will also be provided at no cost while you take part in this study.

Most of the tests, procedures, and/or drugs provided to you are routinely used to treat your illness. You would receive these tests, procedures, and/or drugs even if you were not participating in this study. You and /or your health plan/insurance will need to pay for this routine care. You will also be responsible for any co-payments or deductibles required by your insurance. Some health plans/insurance companies will not pay the costs associated with these tests, procedures, and/or drugs. Financial counseling and itemized cost estimates are available upon request.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?
It is important that you promptly tell the researchers if you believe that you have been injured because of taking part in this study. You can tell the researcher in person or call him/her at the number listed at the top of this form.

If you are injured as a result of being in this study, UCI will provide necessary medical treatment. The costs of the treatment may be covered by the University of California or billed to you or your insurer just like other medical costs, depending on a number of factors. The University does not normally provide any other form of compensation for injury. For more information about this, you may call UCI Human Research Protections (949) 824-6068 or (949) 824-2125 or by e-mail at IRB@research.uci.edu

WHAT HAPPENS IF I WANT TO STOP TAKING PART IN THIS STUDY?
You are free to withdraw from this study at any time. **If you decide to withdraw from this study, you should notify the research team immediately**. The research team may also end your participation in this study if you do not follow instructions, miss scheduled visits, the study sponsor decides to stop the study or your safety and welfare are at risk.

If you experience any of the side effects listed above, if your health worsens, or if you are injured during the research, you may need to be withdrawn from the study, even if you would like to continue. The research team will make this decision and let you know if it is not possible for you to continue. The decision may be made to protect your safety and welfare, or because the research plan does not allow people who develop certain conditions to continue to participate.

If you withdraw or are removed from the study, the researcher may ask you to return for a final visit and follow up with you in the clinic or by phone at least every 6 months to check on your health status.

1. If you elect to withdraw or are withdrawn from this FDA-regulated research study, the data collected from your participation in this study must remain in the trial database in order for the study to be scientifically valid.

HOW WILL INFORMATION ABOUT ME AND MY PARTICIPATION BE KEPT?
Subject Identifiable Data
Some identifiable information collected about you will be removed and replaced with a code. A list linking the code and your identifiable information will be kept separate from the research data.

Data Storage
Research data will be maintained in paper format in a secure location at UCI.

Research data will be stored electronically on a secure network in an encrypted file with password protection.

Data Retention
Research data will be kept on file until three years after the completion of the final study report of this study.

WHO WILL HAVE ACCESS TO MY STUDY DATA?
The research team, authorized UCI personnel, and regulatory entities such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP), may have access to your study records to protect your safety and welfare.

While the research team will make every effort to keep your personal information confidential, it is possible that an unauthorized person might see it. We cannot guarantee total privacy.

Future Research Use
Your information may be used for future research still to be planned. Possible future research studies may include, for example:

- Studying factors associated with benefit from the study medication

You will not be informed about any of the specific research studies that might be conducted with your information. This means that your information could be used in research in which you might not have chosen to participate (i.e. without your additional consent).

Sharing for Future Research
Any information shared for future research will **not** include your name or other personal identifying information.

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

Clinical Trials Reporting Program
UCI's NCI-Designated Cancer Center or the Sponsor registers National Cancer Institute (NCI)-supported clinical trials with NCI though their Clinical Trials Reporting Program (CTRP) to provide study related information. The data provided will include the following identifiable information that may identify you: birth month/year and five-digit zip code. NCI uses the data to manage and enhance the nation's investment in cancer research.

Investigator Financial Conflict of Interest
No one on the study team has a disclosable financial interest related to this research project.

Genetics
In the event of an unexpected breach of confidentiality, a federal law called the Genetic Information Non-Discrimination Act (GINA) will help protect you from health insurance or employment discrimination based on genetic information obtained about you. In California, state law (CalGINA) requires that employers with 5 or more employees may not use your genetic information, obtained from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment. However, these laws do not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

If you would like more information about the federal GINA law go to:
http://www.genome.gov/Pages/PolicyEthics/GeneticDiscrimination/GINAInfoDoc.pdf or CalGINA:
http://www.leginfo.ca.gov/pub/11-12/bill/sen/sb_0551-0600/sb_559_bill_20110906_chaptered.pdf

ARE THERE OTHER ISSUES TO CONSIDER IN DECIDING WHETHER TO PARTICIPATE IN THIS STUDY?

Use of Biospecimens

Biospecimens (such as blood, tissue, or saliva) collected from you for this study and/or information obtained from your biospecimens may be used in this research or other research, and shared with other organizations. You will not share in any commercial value or profit derived from the use of your biospecimens and/or information obtained from them.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

If you have any comments, concerns, or questions regarding the conduct of this research, please contact the research team listed at the top of this form.

A 24-hour number is also listed on the top of this form to report any health concerns or unanticipated problems you may experience after normal hours or on weekends.

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any suggestions, problems or concerns you may have about the study, please contact the UCI Institutional Review Board by phone, (949) 824-6068 or (949) 824-2125, by e-mail at IRB@research.uci.edu or at 160 Aldrich Hall, Irvine, CA 92697-7600.

What is an IRB? An Institutional Review Board (IRB) is a committee made up of scientists and non-scientists. The IRB's role is to protect the rights and welfare of human subjects involved in research. The IRB also assures that the research complies with applicable regulations, laws, and institutional policies.

HOW DO I AGREE TO PARTICIPATE IN THIS STUDY?

You should not sign and date this consent form until all of your questions about this study have been answered by a member of the research team listed at the top of this form. You will be given a copy of this signed and dated consent form, and the attached "Experimental Subject's Bill of Rights" to keep. **Participation in this study is voluntary.** You may refuse to answer any question or discontinue your involvement at any time without penalty or loss of benefits to which you might otherwise be entitled. Your decision will not affect your future relationship with UCI or your quality of care at the UCI Medical Center.

If, during the course of this study, significant new information becomes available that may relate to your willingness to continue to participate, this information will be provided to you by the research team listed at the top of the form.

Your signature below indicates you have read the information in this consent form and have had a chance to ask any questions you have about this study.

Note: As the research described in this form involves your protected health information (PHI), you will be asked to sign separate UC HIPAA Research Authorization form for the use of your PHI.

I agree to participate in the study.

_____ _____
Subject Signature **Date**

_____
Printed Name of Subject

_____ _____
Signature of Person Obtaining Informed Consent **Date**
(For research that is greater than minimal risk, this individual must be listed on Page 1 of this consent)

_____
Printed Name of Person Obtaining Informed Consent

A witness signature is required on this consent form only if: ***(Researchers: check which one applies)***

IMPORTANT! If no witness signature is required, this witness signature section of the consent form may be left blank.

☐ Consent is obtained from the subject via the Short Form process, as approved by the IRB.
☐ The subject has decision-making capacity, but cannot read, write, talk or is blind.
☐ The subject's guardian/legally authorized representative (LAR) cannot read, write, talk or is blind.
☐ The IRB specifically mandated a witness signature for this study (e.g., high risk and/or invasive research procedures).

For the witness:
I confirm that the information in this consent form was accurately explained to and understood by the subject or legally authorized representative and that informed consent was given freely.

_____ _____
Witness Signature **Date**
Note: The witness must be impartial (i.e. not a member of the subject's family, not a member of the study team).

_____
Printed Name of Witness

UNIVERSITY OF CALIFORNIA, IRVINE
Experimental Subject's Bill of Rights

The rights listed below are the right of every individual asked to participate in a research study. You have the right:

1. To be told about the nature and purpose of the study.

2. To be told about the procedures to be followed in the research study, and whether any of the drugs, devices, or procedures is different from what would be used in standard practice.

3. To receive a description of any side effects, discomforts, or risks that you can reasonably expect to occur during the study.

4. To be told of any benefits that you may reasonably expect from the participation in the study, if applicable.

5. To receive a description of any alternative procedures, drugs, or devices that might be helpful, and their risks and benefits compared to the proposed procedures, drugs or devices.

6. To be told of what sort of medical treatment, if any, will be available if any complications should arise.

7. To be given a chance to ask any questions concerning the research study both before agreeing to participate and at any time during the course of the study.

8. To refuse to participate in the research study. Participation is voluntary. You may refuse to answer any question or discontinue your involvement at any time without penalty or loss of benefits to which you might otherwise be entitled. Your decision will not affect your right to receive the care you would receive if you were not in the experiment.

9. To receive a copy of the signed and dated written consent form and a copy of this form.

10. To be given the opportunity to freely decide whether or not to consent to the research study without any force, coercion, or undue influence.

If you have any concerns or questions regarding the research study you should contact the research team listed at the top of the consent form.

If you are unable to reach a member of the research team and have general questions, or you have concerns or complaints about the research study, research team, or questions about your rights as a research subject, please contact the UCI's Human Research Protections unit in the Office of Research by calling (949) 824-6068 or (949) 824-2125 Monday – Friday, 8 am – 5 pm; or by e-mail at IRB@research.uci.edu; or by writing us at 160 Aldrich Hall, Irvine, CA 92697-7600.

UCI IRB# **2020-5660**

University of California Irvine Health

Permission to Use Personal Health Information for Research

Study Title (or IRB Approval Number if study title may breach subject's privacy):

UCI 18-79: A Phase II Open Label Trial of Neo-Adjuvant Abemaciclib with Fulvestrant in Patients Who Develop Localized Recurrence While on Adjuvant Endocrine Therapy with Molecular Evidence of Endocrine Resistance

Principal Investigator Name:

Ritesh Parajuli, MD

Sponsor/Funding Agency (if funded):

UC Irvine

A. What is the purpose of this form?

State and federal privacy laws protect the use and release of your health information. Under these laws, the University of California or your health care provider cannot release your health information for research purposes unless you give your permission. Your information will be released to the research team which includes the researchers, people hired by the University or the sponsor to do the research and people with authority to oversee the research. If you decide to give your permission and to participate in the study, you must sign this form as well as the Consent Form. This form describes the different ways that health care providers can share your information with the researcher, research team, sponsor and people with oversight responsibility. The research team will use and protect your information as described in the attached Consent Form. However, once your health information is released by UC Irvine Health it may not be protected by the privacy laws and might be shared with others. If you have questions, ask a member of the research team.

B. What Personal Health Information will be released?

If you give your permission and sign this form, you are allowing your health care provider to release the following medical records containing your Personal Health Information. Your Personal Health Information includes health information in your medical records, financial records and other information that can identify you.

☒ Entire Medical Record

☐ Ambulatory Clinic Records

☐ Progress Notes

☐ Other Test Reports

☐ Other (describe):

_____

(Description of Other Health Information)

☐ Lab & Pathology Reports

☐ Dental Records

☐ Operative Reports

☐ Discharge Summary

☐ Consultations

☐ Emergency Department Records

☐ Financial Records

☐ Imaging Reports

☐ History & Physical Exams

☐ Psychological Tests

C. Do I have to give my permission for certain specific uses?

Yes. The following information will only be released if you give your specific permission by putting your initials on the line(s).

_____I agree to the release of information pertaining to drug and alcohol abuse, diagnosis or treatment.

_____I agree to the release of HIV/AIDS testing information.

_____I agree to the release of genetic testing information.

_____I agree to the release of information pertaining to mental health diagnosis or treatment.

D. Who will disclose and/or receive my Personal Health Information?

Your Personal Health Information may be shared with these people for the following purposes:

1. To the research team for the research described in the attached Consent Form;
2. To others at UC with authority to oversee the research
3. To others who are required by law to review the quality and safety of the research, including: U.S. government agencies, such as the Food and Drug Administration or the Office of Human Research Protections, the research sponsor or the sponsor's representatives, or government agencies in other countries.

E. How will my Personal Health Information be shared for the research?

If you agree to be in this study, the research team may share your Personal Health Information in the following ways:

1. To perform the research
2. Share it with researchers in the U.S. or other countries;
3. Use it to improve the design of future studies;
4. Share it with business partners of the sponsor; or
5. File applications with U.S. or foreign government agencies to get approval for new drugs or health care products.

F. Am I required to sign this document?

No, you are not required to sign this document. You will receive the same clinical care if you do not sign this document. However, if you do not sign the document, you will not be able to participate in this research study.

G. Optional research activity

If the research I am agreeing to participate in has additional optional research activity such as the creation of a database, a tissue repository or other activities, as explained to me in the informed consent process, I understand I can choose to agree to have my information shared for those activities or not.

☐ I agree to allow my information to be disclosed for the additional optional research activities explained in the informed consent process.

H. Does my permission expire?

This permission to release your Personal Health Information expires when the research ends and all required study monitoring is over.

I. Can I cancel my permission?

You can cancel your permission at any time. You can do this in two ways. You can write to the researcher or you can ask someone on the research team to give you a form to fill out to cancel your permission. If you cancel your permission, you may no longer be in the research study. You may want to ask someone on the research team if canceling will affect your medical treatment. If you cancel, information that was already collected and disclosed about you may continue to be used for limited purposes. Also, if the law requires it, the sponsor and government agencies may continue to look at your medical records to review the quality or safety of the study.

J. Signature

Subject

If you agree to the use and release of your Personal Health Information, please print your name and sign below. You will be given a signed copy of this form.

_____

Subject's Name (print)—*required*

_____ _____

Subject's Signature Date

Parent or Legally Authorized Representative

If you agree to the use and release of the above named subject's Personal Health Information, please print your name and sign below.

Parent or Legally Authorized Representative's Name (print)	Relationship to Subject
Parent or Legally Authorized Representative's Signature	Date

Witness

If this form is being read to the subject because s/he cannot read the form, a witness must be present and is required to print his/her name and sign here:

Witness' Name (print)	
Witness' Signature	Date