

THOMAS JEFFERSON UNIVERSITY  
Sidney Kimmel Cancer Center

*A Phase II clinical trial evaluating the combination of onapristone with anastrozole for women with hormone receptor positive endometrial cancer*

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### Signature Page

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 US federal regulations and ICH guidelines.

Principal Investigator:

Signed: \_\_\_\_\_ Date: \_\_\_\_\_

Name: Tommy Buchanan, MD

Title: Assistant Professor, Division of Gynecology Oncology, Department of Obstetrics  
and Gynecology

### Statement of Compliance

This study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and Thomas Jefferson University research policies

## List of Abbreviations

|         |                                                             |
|---------|-------------------------------------------------------------|
| AE      | Adverse Event/Adverse Experience                            |
| CFR     | Code of Federal Regulations                                 |
| CIOMS   | Council for International Organizations of Medical Sciences |
| CONSORT | Consolidated Standards of Reporting Trials                  |
| CRF     | Case Report Form                                            |
| CRO     | Clinical Research Organization                              |
| CTCAE   | Common Terminology Criteria for Adverse Events              |
| DCR     | Disease Control Rate                                        |
| DOR     | Duration of Response                                        |
| DSMC    | Data and Safety Monitoring Committee                        |
| DSMP    | Data and Safety Monitoring Plan                             |
| FDA     | Food and Drug Administration                                |
| FWA     | Federalwide Assurance                                       |
| GCP     | Good Clinical Practice                                      |
| GWAS    | Genome-Wide Association Studies                             |
| HIPAA   | Health Insurance Portability and Accountability Act         |
| IB      | Investigator's Brochure                                     |
| ICF     | Informed Consent Form                                       |
| ICH     | International Conference on Harmonisation                   |
| IHC     | Immunohistochemistry                                        |
| IND     | Investigational New Drug Application                        |
| IRB     | Institutional Review Board                                  |
| MedDRA  | Medical Dictionary for Regulatory Activities                |
| MOP     | Manual of Procedures                                        |
| N       | Number (typically refers to participants)                   |
| NCI     | National Cancer Institute                                   |
| NIH     | National Institutes of Health                               |
| OHRP    | Office for Human Research Protections                       |
| PHI     | Protected Health Information                                |
| PI      | Principal Investigator                                      |
| PRC     | Protocol Review Committee                                   |
| QA      | Quality Assurance                                           |
| QC      | Quality Control                                             |
| SAE     | Serious Adverse Event/Serious Adverse Experience            |

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|      |                                                               |
|------|---------------------------------------------------------------|
| SDS  | Safety Data Sheet (formerly MSDS; Material Safety Data Sheet) |
| SKCC | Sidney Kimmel Cancer Center                                   |
| SOP  | Standard Operating Procedure                                  |
| TJU  | Thomas Jefferson University                                   |
| UAP  | Unanticipated Problem                                         |

## Study Summary

**Title:** A Phase II clinical trial evaluating the combination of onapristone with anastrozole for women with hormone receptor positive endometrial cancer

**Précis:** This is a multi-center phase II clinical trial investigating the PR antagonist onapristone with anastrozole to treat ER+/PR+ endometrial cancer patients

**Objectives:**

**Co-Primary:**

- Objective response rate (ORR) using RECIST v.1.1 and
- 4-month progression free survival (PFS)

**Secondary:**

- To estimate the disease control rate (DCR)
- To describe duration of response (DOR)
- To evaluate the safety and tolerability of combination therapy
- To evaluate quality of life using the Edmonton Symptom Assessment questionnaire.

**Exploratory:**

- To characterize the ER and PR expression by IHC pre- and post-treatment.

**Population:** Women  $\geq 18$ yo with ER+/PR+ endometrial adenocarcinoma

**Phase:** Phase II

**Number of Sites:** 3: Thomas Jefferson University Hospital, Abington Hospital – Jefferson Health, Jefferson- South Jersey

**Description of Intervention:** Onapristone ER 50 mg PO BID + anastrozole 1 mg PO QD

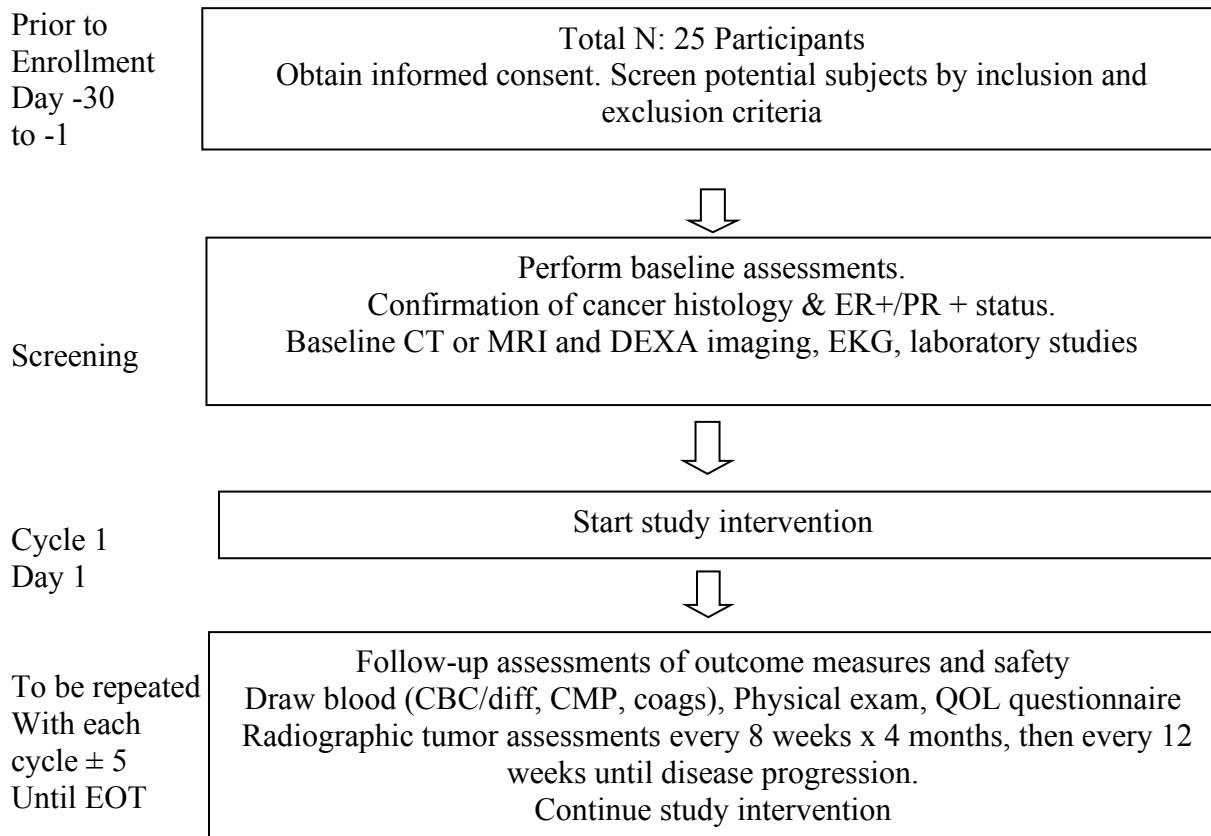
**Study Duration:** Until November 30th, 2023, or disease progression, or an adverse event that requires patient to be removed from study

**Participant Participation Duration:** Until November 30th, 2023, or disease progression, or an adverse event that requires patient to be removed from study. If a patient is removed from the study for an event other than disease progression, they will be followed every 3 months for survival follow up. If patients are without disease progression on November 30th, 2023,

they will be followed every 3 months for survival follow up until the time of first disease progression.

**Estimated Time to Complete Enrollment:** Estimated time to complete enrollment is 24 months.

### Schematic of Study Design:



## 1 Introduction

### 1.1 Background Information

Endometrial cancer is the most common gynecologic malignancy in the United States with an incidence that continues to increase each year. More than 60,000 women were diagnosed with endometrial cancer in 2018 and this disease contributes to more than 10,000 deaths annually (Siegel et al., 2019). Unopposed estrogen production and obesity are the most common risk factors for the development of endometrial cancer; both late stage disease and histologic subtype portends to a poor prognosis with a five-year survival of only 20% (Lewin et al., 2010). In the second line setting, cytotoxic chemotherapy has a 13% response rate (Miller et al., 2018) and hormonal therapy with anastrozole has a response rate of 9% (Rose et al., 2000). For a minority of patients with MSI-high endometrial cancer (about 30% of patients), pembrolizumab is a therapeutic option and results in an overall response rate of 39% in 149 patients across 15 tumor types with 78% of responses lasting greater than 6 months and has led to FDA approval of this single agent in tissue agnostic cases (Ott et al., 2018). Megesterol acetate is approved in the second line setting with response rates as high as 24% in conjunction with tamoxifen, but is not commonly used due to poor tolerance and high risk of thrombosis (Fiorica et al., 2004). The majority of patients with recurrent endometrial cancer have limited therapeutic options and the development of second line therapies that result in improved response is an unmet clinical need. Using targeted hormonal treatment may present potential opportunities for improved treatment outcomes for these women.

### **The Progesterone Receptor (PR) as a Target for Treatment**

The Progesterone Receptor (PR) belongs to the steroid receptor family and is a ligand-activated transcription factor which plays a key role in hormonally regulated tissues such as endometrial, breast, and prostate cancer (Bregar et al., 2014). PR is expressed in normal cells and in certain malignant tissues, mediating the effects of progesterone by association with a range of co-regulatory proteins and binding to specific target sequences in progesterone-regulated gene promoters. Ligand activation of PR results in redistribution into discrete sub-nuclear PR foci that are detectable by immunofluorescence representing aggregates or clusters of multiple transcriptionally active PR-co-regulator complexes. PR foci are aberrant in cancers, suggesting that the co-regulator composition and number of complexes is altered. As a consequence, the PR is considered a relevant therapeutic target for further study (Faivre and Lange, 2007; Hagan et al., 2011; Jonat et al., 2013; Scarpin et al., 2009).

The expression of the progesterone receptor (PR) has been well described in endometrial cancers and anti-progestins have been shown to have anti-tumor properties and an inhibitory effect on the growth of these cancer cells in preclinical models (Thigpen et al., 1999). PR is a ligand activated transcription factor which plays a key role in hormonally regulated tissues. Studies have shown that tumors with a transcriptionally active PR co-regulatory complex (APR pattern) are predominantly present on endometrial tumors (Zukiwski et al., 2015). Activation of PR by

phosphorylation causes downstream signaling of MAPK, CDK, MEK, EGF, and other growth factors that promote tumor growth. (Daniel et al., 2011).

### **PR Isoforms and Activated PR (APR)**

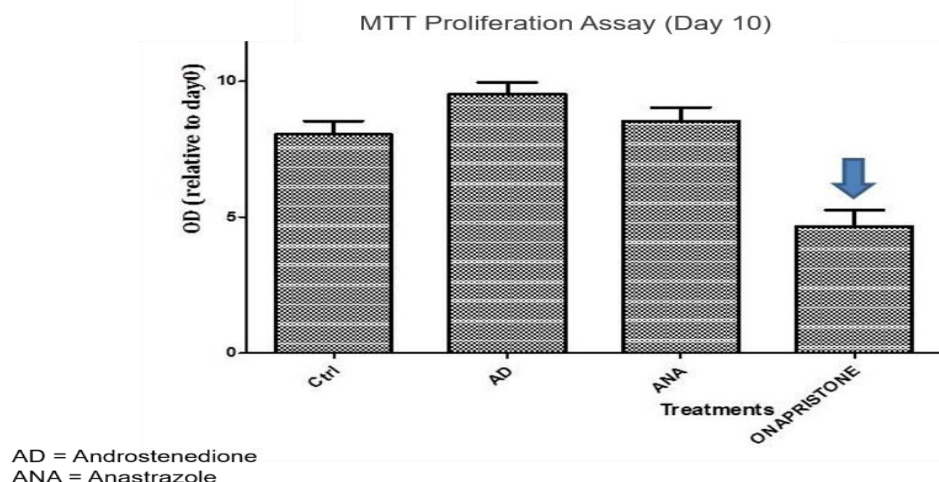
The PR is expressed as two main forms (PRA and PRB) with different molecular weights and functions. In normal human tissues, expression of PRA and PRB is balanced, while in malignant tissues e.g. breast, endometrial and prostate cancer, the proportion of PRA and PRB may be profoundly altered: PR isoform predominance, especially PRA predominance, is evident in a significant proportion of ductal carcinoma in situ (DCIS) and invasive cancers. In addition another distinctive feature of malignancy is that there is marked heterogeneity of PRA:PRB expression between neighboring cells, as demonstrated in breast, prostate and endometrial cancers. PRB is predominant in endometrial cancer (Arnett-Mansfield et al., 2004; Mote and Clarke, 2000; Sasaki, 2002; Scarpin et al., 2009)

### **Onapristone Background**

Onapristone is a type 1 anti-progestin which prevents the PR from dimerizing (Allan et al., 1992) and does not result in ligand-induced phosphorylation of the PR (Beck et al., 1996; Clemm et al., 2000). This is in contrast to other anti-progestins (Afhüppe et al., 2009; Beck et al., 1996). Non-dimerized PR does not form nuclear PR foci and therefore does not bind to DNA (Graham et al., 2009). This aspect is key to the activity of onapristone, as dimerization is necessary for binding with the co-activators and subsequently to PRE in PR-dependent genes. Without functional PR dimers and PRE binding, no PR-dependent gene transcription can occur. Studies have been conducted to examine the ability of PR to recruit a chromatin-remodeling complex to the promoter when bound to different classes of antagonists and the influence of this interaction on PR dynamics and function in vivo (Arnett-Mansfield et al., 2007).

Apristor, an extended release onapristone, is a type I pure progesterone receptor antagonist that inhibits progesterone hormone-mediated PR activation and stabilizes PR association with corepressors. Onapristone was compared with anastrozole and androstenedione in an MTT proliferation assay in the MCF7 tamoxifen-resistant cell line. The study showed that onapristone reduced the proliferative index of the cancer cells by approximately 50% vs control or either of the other hormonal agents as seen below in **Figure 1** [Fuqua, S. 2019].

**Figure 1: Onapristone activity in MCF7 tamoxifen-resistant cell line**



Onapristone is also active in T47D cell lines stimulated by either progesterone or estradiol in steroid-free serum, but not in other PR-positive cell lines. It is hypothesized that tumors with APR pattern may benefit from the PR antagonist, Onapristone.

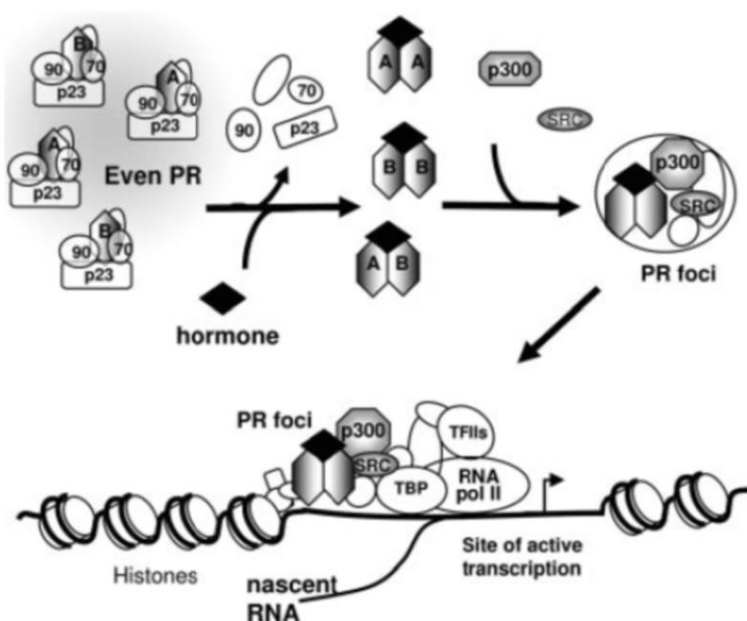
In vitro studies confirmed that the principal metabolite is mono-demethylated onapristone (M1) and the metabolism is biphasic. The majority of onapristone metabolism is via CYP3A4, leading to the potential for drug-drug interactions in the clinical setting. There is also evidence that onapristone induces CYP3A4.

Pre-clinical pharmacokinetic (PK) and pharmacodynamic (PD) studies have demonstrated that onapristone is well absorbed, with extensive distribution into tissues and very high protein-binding (99.5% in human plasma). Historic data in humans has reported  $t_{1/2}$  to be between 2-4 hours, which is similar to that observed in cynomolgus monkeys (3h). In the monkeys the clearance of onapristone was considered moderate.

The PK and food effect study results from a phase I study in healthy subjects observed a half-life ( $t_{1/2}$ ) of 4.2h for an oral immediate-release (IR) formulation of onapristone administered in fasting conditions. The same study observed a minor food effect on the maximum plasma concentration ( $C_{max}$ ) of onapristone and its metabolite M1 with an approximate average decrease of 18% and an average increase in  $AUC_{\infty}$  of approximately 13%.

Upon ligand (e.g. progesterone) binding, the PR dimerizes and attracts nuclear cofactors to form a complex. This complex becomes functional and binds to specific DNA sequences in the promoters of PR-dependent genes, termed Progesterone Response Elements (PRE). The DNA PRE binding is an energy requiring process and is associated with chromatin remodeling (Rayasam et al., 2005). A simplified diagram of the proposed subnuclear distribution of the PR is illustrated below in **Figure 2**.

**Figure 2: Proposed Model of Subnuclear Distribution of PR Isoforms (Arnett-Mansfield et al., 2007)**

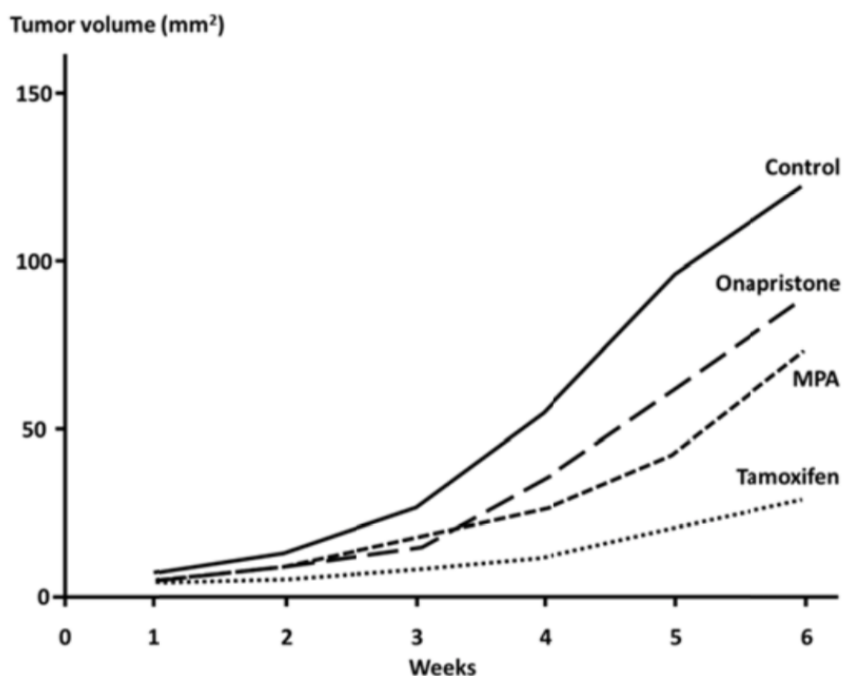


## Pre-Clinical Studies with Onapristone

Nishino et al. found an antitumor effect of onapristone on rat Dunning tumors. Their finding of PR in prostate and prostatic tumors confirms other data and suggests the involvement of progesterone in the mechanism of hormone-dependent growth of prostate and tumors. Orchiectomized rats were treated subcutaneously daily with progesterone, dihydrotestosterone (DHT), estradiol, onapristone, ICI 182780 (a pure anti-estrogen) or flutamide for 12 days. After the last treatment, animals were sacrificed, and the organ weight of ventral prostate (VP) and dorsolateral prostate (DLP) was determined. Progesterone increased the organ weight of VP and DLP in a dose-dependent manner. In contrast to DHT, which preferentially stimulated the growth of VP, progesterone led to an increase in the weight of DLP. The effect of progesterone on the DLP was enhanced by a simultaneous application of DHT or estradiol. Onapristone and the pure antiestrogen had no appreciable effect on the progesterone-induced growth of VP and DLP. However, onapristone inhibited the estrogen/progesterone-induced growth of DLP without affecting the growth of the VP. In contrast, the antiandrogen flutamide suppressed the stimulatory effect of progesterone on both the VP and DLP. The authors suggested that the stimulatory effect of progesterone may be due to both androgenic products derived from progesterone, and a PR-mediated mechanism (Nishino et al., 2009).

A limited preclinical study was conducted in a prophylaxis model using nude mice xenografted with an endometrial cell line taken from one patient with ER positive and borderline PR positive endometrial carcinoma (Rudoreanu, 1993). Tumor cells passaged several times after removal from one patient's endometrial tumor were implanted into nude mice and stimulated with estradiol for 1 week prior to administration of the study agents (vehicle, onapristone, MPA and tamoxifen) weekly for 6 weeks.

**Figure 3: Effect of Onapristone in an ER-positive, PR-indeterminate Xenograft Prevention Model of Endometrial Carcinoma**



There was a 50% reduction in tumor growth with onapristone in comparison to the control which was comparable to that of MPA. Several animal models have shown that anti-progestins were able to inhibit tumor growth as single agents, in progestin-induced or 7,12-dimethylbenz(α)anthracene (DMBA)-induced, estrogen-induced and even in progestin-induced but progestin-growth independent tumors. It seems that the direct antagonism of PR is critical for growth inhibition, as shown recently with the use of PR antisense oligodeoxynucleotides. In one study, BALB/c mice with subcutaneous 25 mm<sup>2</sup> mammary carcinomas expressing ERα and PR were injected intraperitoneally with PR antisense oligos every 24 or 12 hours for 5-10 days, or continuous mifepristone subcutaneously once every 24 hours or once as a subcutaneous implant. Control mice received vehicle or scrambled oligonucleotide to PRs. Tumor growth was inhibited by PR antisense oligos and mifepristone, and the authors concluded that this provided further evidence for a critical and hierarchical role for the PR pathway in mammary carcinomas (Lamb et al., 2005).

### Phase I Trial with Single Agent Onapristone

A Phase 1 pilot study conducted by Context Therapeutics showed treatment with Onapristone improved PFS in endometrial adenocarcinoma patients who received previous treatment with

chemotherapy (**Table 1**). Of the 8 patients enrolled on the trial with endometrial cancer, the average improvement in PFS was about 3.5 months. One patient with metastatic lesions to the lung and bone appeared to have a PFS of 12.0 months.

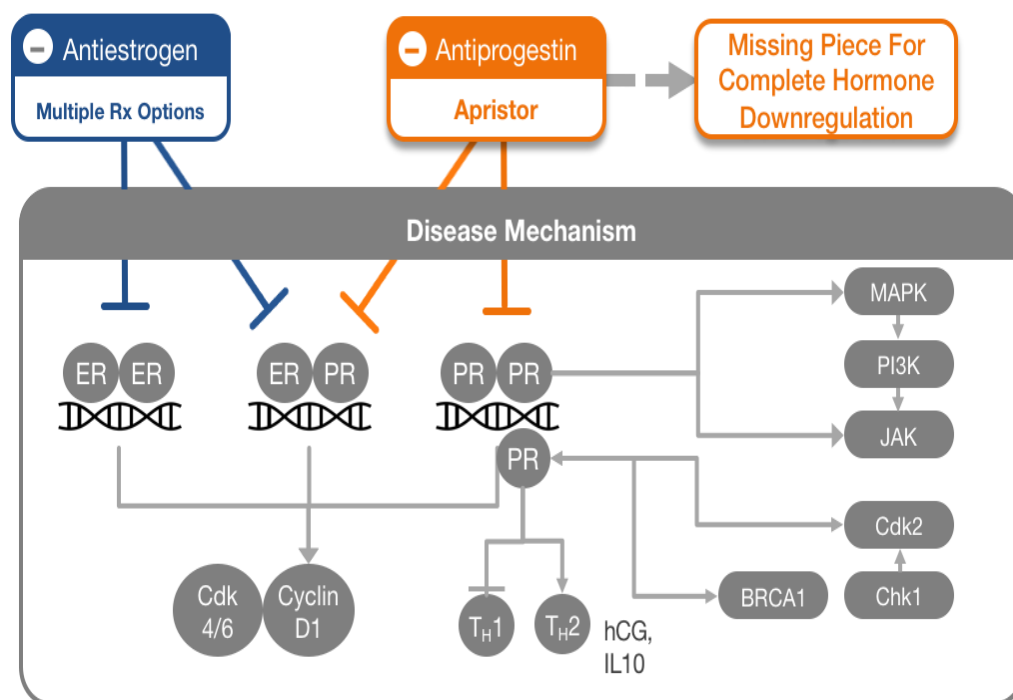
**Table 1:**

| Patient # | Subtype                     | Dose (mg) | PFS (mos) | Metastatic Site(s)                | Prior Rx (N) | Treatment Sequent (PFS, months)                         |
|-----------|-----------------------------|-----------|-----------|-----------------------------------|--------------|---------------------------------------------------------|
| 1-8       | Endometrium Adenocarcinoma  | 30        | 12.0      | Bone, Lung                        | 3            | C + T (5), RT (6), G + O (3)                            |
| 3-8       | Endometrium Carcinoma       | 20        | 8.3       | Lung, Pelvis                      | 3            | RT (24), C + T (11), LPD (7)                            |
| 6-16      | Endometrial Stromal Sarcoma | 40        | 4.0       | Node, Lung                        | 2            | D + C + I (8), F (4)                                    |
| 6-8       | Uterine Leiomyosarcoma      | 20        | 4.0       | Liver, Lung, Peritoneum, Pleura   | 5            | RT (13), D + I (18), G (3), CP (10), DC (6)             |
| 6-9       | Uterine Leiomyosarcoma      | 30        | 2.0       | Bone, Lung                        | 6            | C + T (12), EP (64), AD + I (4), G (3), DC (10), RE (2) |
| 6-10      | Uterine Adenocarcinoma      | 50        | 2.0       | Bone, Lung, Node, Uterus          | 1            | M + Z (7)                                               |
| 6-15      | Endometrium Carcinoma       | 20        | 2.0       | Bone, Lung                        | 3            | RT (14), 7 (29), D + C (5)                              |
| 8-7       | Endometrium Adenocarcinoma  | 10        | 2.0       | Peritoneum                        | 2            | C + P (7), M (2)                                        |
| 6-4       | Uterine Sarcoma             | 50        | 2.0       | Lung, Peritoneum                  | 2            | RT (36), C + T (22)                                     |
| 3-13      | Endometrium Carcinoma       | 20        | 1.6       | Liver, Peritoneum, Vagina         | 4            | RT (4), C + T (4), D (3), T (2)                         |
| 6-14      | Endometrium Adenocarcinoma  | 10        | 1.2       | Liver, Lung, Node, Pleura, Uterus | 4            | C + T (4), RT (20), T (4), C (2)                        |
| 2-10      | Endometrium Carcinoma       | 20        | 1.0       | Node, Peritoneum, Soft Tissue     | 3            | C + T (12), M (2), LPD (9)                              |

Onapristone has been shown to be overall well tolerated without significant adverse events. Under the Context Therapeutics development program to date, 12 healthy female volunteers have received a single dose of 10 mg immediate release (IR) onapristone, 31 male patients with prostate cancer and 52 females with PR-positive breast, ovarian, and endometrial tumors have received doses of 10-50 mg onapristone ER BID or 100 mg/day of onapristone IR (Jonat and Giurescu, 2002). There were no grade 4 treatment-related AEs reported to date. The majority of adverse events were grade 1 or 2. Grade 3 adverse events were reported in 12 patients (16%) patients: GGT increase (5%), AP and AST increases (3% each), and nausea and anorexia (1% each). The most common related AEs reported (all grades) were asthenia (16%), GGT increase (15%), nausea (14%), AST increase (12%), and ALT increase (11%). Two patients discontinued onapristone due to AEs. One patient discontinued due to three AEs including anemia, thrombocytopenia and leukopenia in the context of bone marrow failure due to progressive bone metastases. The other patient had a 25% dose reduction for hepatic toxicity and subsequently discontinued onapristone due to disease progression/LFT abnormalities. One death has been reported occurring within 30 days of discontinuing onapristone as a result of respiratory distress due to progression of lung metastases.

This promising phase I data led to hypotheses regarding combination therapy that are being investigated as seen in **Figure 4**.

**Figure 4:**



### Prior Clinical Data with Onapristone from Breast Cancer Studies:

A non-randomized, open, multicenter phase 2 study was conducted between December 1991 and May 1995 at 13 sites in Germany and the United Kingdom (Jonat and Giurescu, 2002). The study goal was to investigate the efficacy and safety of onapristone when given 100 mg/day to post-menopausal women with advanced breast cancer that had progressed on tamoxifen. Of the 101 evaluable patients, one had a complete response (CR), 9 had a partial response (PR), and 39 had SD for three months or more. This resulted in an overall clinical benefit of 49%. The median duration of the CR + PR was 11 months and the median duration for patients with SD was seven months. The responses seen in the group of 33 evaluable patients with PR-positive primary tumors were promising with 4 (12%) patients displaying a partial response, 15 (45%) patients with stable disease.

A phase 2 study investigating onapristone as first-line endocrine therapy in patients with breast cancer was conducted as an investigator initiated study (Robertson et al., 1999). The study enrolled 19 patients before Schering AG closed the study in 1995 when the decision was made to halt the development of the immediate release formulation of onapristone. Of the 19 patients entered into the study prior to study closure, one discontinued therapy after 4.5 months because of a marked elevation in the patient's LFT's. At that time, the patient had SD. The elevated LFTs rapidly returned to normal after discontinuation of onapristone. Of the remaining 18 patients, the

overall tumor benefit rate was 67%. The median duration of objective response and SD was 16.2 months. The majority of patients had hormone-receptor-positive tumors. Ten patients were ER-positive/PR-positive, of whom seven achieved PR, 1 had SD. Six patients had ER-positive/PR-negative tumors, of whom two achieved PR and two had SD. No response was seen in the remaining two patients who had ER-negative/PR-negative tumors.

### **Prior Clinical Data with Onapristone from Ovarian Cancer Studies:**

A phase I dose escalation study of onapristone ER in progesterone receptor positive (PR+) breast, endometrial, and ovarian cancer patients found all doses tested to be safe and well tolerated, with 50mg PO BID recommended as the phase 2 dose. The most common treatment-related adverse events reported were nausea, fatigue and constipation. In that phase I study patients with heavily pretreated granulosa cell ovarian cancer, low grade serous ovarian cancer, and endometrial cancer were seen to have tumor stabilization for at least 16 weeks (Cottu et al., 2018). These are hormonally driven gynecologic cancers which generally have poor responses to chemotherapy and limited treatment options.

While prospective data are lacking in patients with low grade serous ovarian cancer, the retrospective response rate to chemotherapy is 4%, and 9% to available hormone therapies (Gershenson et al., 2012, 2009). The most common type of sex-cord stromal ovarian cancer, generally has poor response rates to chemotherapy and is commonly treated with hormonal strategies in the recurrent setting based on retrospective data. The first prospective study of anastrozole in patients with recurrent ER/PR + granulosa cell tumors was recently reported and demonstrated a 2.5% response rate, clearly demonstrating a need for further treatment options for this disease (Banerjee et al., 2018).

### **Recurrent Endometrial Cancer: An unmet clinical need**

Recurrent endometrial cancer has limited treatment options with a 13% response rate to chemotherapy (Miller et al., 2018). Megestrol acetate is approved in the recurrent setting and has shown response rates as high as 24% in conjunction with tamoxifen in the recurrent setting, but is not commonly used due to poor tolerance (Gershenson et al., 2012). Additionally, hormonal therapy with Anastrozole results in a 9% response rate. Patients with MSI high endometrial cancer have the option of treatment with pembrolizumab (about 30% of all endometrial cancer patients). However, patients with microsatellite stable endometrial cancer have few therapeutic options in the second-line setting. Apristor (onapristone ER) is a well-tolerated oral full progesterone antagonist which has shown promising preliminary findings in gynecologic cancers based on a dose escalation study (Cottu et al., 2018).

### **Onapristone in Combination with Endocrine Therapy**

To date, there are no combinations of endocrine therapies used in the treatment of hormone-sensitive cancers. It is reasonable to assume that an appropriate combination of “hormonal” therapies with different modes of action might be more effective than the respective individual hormonal agents. Several publications discuss the enhancement of the anti-tumor effect of onapristone in combination with pure anti-estrogens, anti-estrogen with partial estrogenic

activity (tamoxifen) or the aromatase inhibitor, exemestane (Klijn et al., 2000; Nishino et al., 1994).

We feel that combination therapy with an ER antagonist and PR antagonist will be highly efficacious in patients with recurrent endometrial cancer. The proposed trial will study the combination of onapristone with anastrozole.

## **1.2 Rationale for the Proposed Study**

We propose to conduct a phase II clinical trial investigating the overall response rate (ORR) and 4-month PFS of onapristone in combination with anastrozole for women with recurrent/metastatic ER/PR+ endometrial carcinoma. We hypothesize that the addition of onapristone to anastrozole will improve the ORR to better than the response rate of current anti-estrogen strategies (9-10%). We also hypothesize that the addition of onapristone to anastrozole will improve the 4-month progression free survival in this population. We plan to treat women with onapristone 50mg PO BID in combination with anastrozole 1 mg PO daily. Secondary endpoints will be disease control rate (DCR), duration of response, evaluate the safety and tolerability, and quality of life using Edmonton Symptom Assessment questionnaire.

## **1.3 Potential Risks and Benefits**

### **1.3.1 Potential Risks**

Trial subjects will be monitored closely for any side effects and will be encouraged and expected to report any new symptoms or developments to the principal investigator or designate. We will also conduct monthly conference calls with all co-investigators at other clinical sites including Abington and Jefferson New Jersey

### **Safety Measurements:**

Safety and tolerability will be determined by frequent assessment of adverse events, physical examinations, vital signs, and safety laboratory assessments as defined in the Study Calendar in Section 6. A safety follow-up visit will be conducted approximately 28days after the last dose of onapristone ER.

### **Toxicities to Date with extended release (ER) Formulation:**

Under the Context Therapeutics development program to date, 12 healthy female volunteers have received a single dose of 10 mg immediate release (IR) onapristone, 31 male patients with prostate cancer and 52 females with PR-positive breast, ovarian, and endometrial tumors have received doses of 10-50 mg onapristone ER BID or 100 mg/day of onapristone IR (Cottu et al., 2018; Jayaram et al., 2017; Rezai et al., 2015).

There were no grade 4 treatment-related AEs reported to date. The majority of adverse events were grade 1 or 2. Grade 3 adverse events were reported in 12 patients (16%) patients: GGT increase (5%), AP and AST increases (3% each), and nausea and anorexia (1% each). The most common related AEs reported (all grades) were asthenia (16%), GGT increase (15%), nausea (14%), AST increase (12%), and ALT increase (11%). Two patients discontinued onapristone due to AEs. One patient discontinued due to three related AEs (anemia, thrombocytopenia and leukopenia) in the context of bone marrow failure due to progressive bone metastases. The other patient had a 25% dose reduction for hepatic toxicity and subsequently discontinued onapristone due to disease progression/LFT abnormalities. One death has been reported within 30 days of discontinuing onapristone; respiratory distress due to progression of lung metastases.

### Potential for Drug-Drug Interaction with Onapristone:

Data have suggested potential drug-drug interactions of onapristone with concomitantly administered CYP3A4 substrates and subsequent non-clinical studies have confirmed that onapristone interacts with midazolam, nifedipine and testosterone, demonstrating both induction and inhibition of CYP3A4, likely attributable to onapristone and its M2 metabolite. Therefore, until more data are available patients should be advised to avoid those agents which are sensitive substrates or strong inducers or inhibitors of CYP3A4 (see Tables below).

Patients will be instructed to use with caution concomitant aspirin, NSAIDs, and prostaglandins. However, the intake of acetaminophen up to 4000 mg/day dosed according to labeling is allowed.

Caution should be exercised when onapristone is administered with drugs that are CYP3A4 substrates and have narrow therapeutic range, including some agents used during general anesthesia.

### CYP3A Enzymes - Classification of Inhibitors

| <b>CyP3A Inhibitors</b> | <b>CyP3A Inducers</b> | <b>CyP3A Substrates</b> |
|-------------------------|-----------------------|-------------------------|
| <b>Strong</b>           | <b>Strong</b>         | <b>Sensitive</b>        |
| Boceprevir              | Avasimibe             | Alfentanil              |
| clarithromycin          | carbamazepine         | Aprepitant              |
| conivaptan              | phenytoin             | Budesonide              |
| grapefruit juice        | rifampin              | buspirone               |
| indinavir               | St. John's wort       | conivaptan              |
| itraconazole            |                       | darifenacin             |
| ketoconazole            |                       | darunavir               |
| lopinavir/ritonavir     |                       | dasatinib               |
| mibefradil              |                       | dronedarone             |
| nefazodone              |                       | eletriptan              |
| nelfinavir              |                       | eplerenone              |
| posaconazole            |                       | everolimus              |
| ritonavir               |                       | felodipine              |

| <b>CyP3A Inhibitors</b> | <b>CyP3A Inducers</b> | <b>CyP3A Substrates</b>          |
|-------------------------|-----------------------|----------------------------------|
| saquinavir              |                       | indinavir                        |
| telaprevir              |                       | fluticasone                      |
| telithromycin           |                       | lopinavir                        |
| voriconazole            |                       | lovastatin                       |
|                         |                       | lurasidone                       |
| <b>Moderate</b>         | <b>Moderate</b>       | maraviroc                        |
| Amprenavir              | Bosentan              | midazolam                        |
| aprepitant              | efavirenz             | nisoldipine                      |
| atazanavir              | etravirine            | quetiapine                       |
| ciprofloxacin           | modafinil             | saquinavir                       |
| darunavir/ritonavir     | nafcillin             | sildenafil                       |
| diltiazem               |                       | simvastatin                      |
| erythromycin            |                       | sirolimus                        |
| fluconazole             |                       | tolvaptan                        |
| fosamprenavir           |                       | tipranavir                       |
| grapefruit juice        |                       | triazolam                        |
| imatinib                |                       | varafenafil                      |
| verapamil               |                       |                                  |
|                         |                       |                                  |
| <b>Weak</b>             | <b>Weak</b>           | <b>Narrow therapeutic window</b> |
| Alprazolam              | Amprenavir            | Alfentanil                       |
| amiodarone              | aprepitant            | astemizole                       |
| amlodipine              | armodafinil           | cisapride                        |
| atorvastatin            | echinacea             | cyclosporine                     |
| bicalutamide            | pioglitazone          | dihydroergotamine                |
| cilostazol              | prednisone            | ergotamine                       |
| cimetidine              | rufinamide            | fentanyl                         |
| cyclosporine            |                       | pimozide                         |
| fluoxetine              |                       | quinidine                        |
| fluvoxamine             |                       | sirolimus                        |
| ginkgo                  |                       | tacrolimus                       |
| goldenseal              |                       | terfenadine                      |
| isoniazid               |                       |                                  |
| nilotinib               |                       |                                  |
| oral contraceptives     |                       |                                  |
| ranitidine              |                       |                                  |
| ranolazine              |                       |                                  |
| tipranavir/ritonavir    |                       |                                  |
| zileuton                |                       |                                  |

FDA Guidance on Drug–Drug Interactions

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm>

### CYP3A Enzymes In vitro:

| CyP3A Inhibitors    | CyP3A Inducers    | CyP3A Substrates            |
|---------------------|-------------------|-----------------------------|
| In vitro inhibitors | In vitro inducers | In vitro substrates         |
| ketoconazole        | rifampin          | midazolam                   |
| itraconazole        |                   | testosterone                |
| azamulin            |                   | erythromycin                |
| troleandomycin      |                   | dextromethorphan            |
| verapamil           |                   | triazolam 4-hydroxylation   |
|                     |                   | terfenadine C-hydroxylation |
|                     |                   | nifedipine oxidation        |

FDA Guidance on Drug–Drug Interactions

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm>

### CYP3A Enzymes In vivo:

| In vivo inhibitors | In vivo inducers | In vivo substrates |
|--------------------|------------------|--------------------|
| atazanavir         | rifampin         | midazolam          |
| clarithromycin     | carbamazepine    | buspirone          |
| indinavir          |                  | felodipine         |
| itraconazole       |                  | lovastatin         |
| ketoconazole       |                  | eletriptan         |
| nefazodone         |                  | sildenafil         |
| nelfinavir         |                  | simvastatin        |
| ritonavir          |                  | triazolam          |
| saquinavir         |                  |                    |
| telithromycin      |                  |                    |

FDA Guidance on Drug–Drug Interactions

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm>

### Potential Toxicities with Anastrozole:

Potential adverse events with anastrozole include but are not limited to:

*Likely (>20%):* Vasodilation and hot flashes

*Less likely (<20%):* Anemia, Leukopenia, Edema, Hypertension, Cataracts, Abdominal pain, Constipation, Diarrhea, Dyspepsia, Nausea, Vomiting, Xerostomia, Fever, Pain, Malaise, Thrombophlebitis, Flu-like syndrome, Weight gain or loss, Hypercholesteremia, Arthralgia, Arthritis, Back pain, Breast pain, Carpal tunnel syndrome, Myalgia, Neck pain, Osteoporosis,

Paresthesia, Weakness Confusion, Dizziness, Fatigue, Headache, Somnolence, Anxiety, Depression, Insomnia, Mood disturbance, Nervousness, Pelvic pain, Urinary tract infection, Vaginal bleeding, Vaginal discharge, Vaginitis, Rhinitis, Pharyngitis, Sinusitis, Alopecia, Pruritis, Rash, Lymphedema

*Rare but serious (<3%):* Angina, Ischemic cerebrovascular event, Myocardial infarction, Venous thromboembolic event, Alkaline phosphatase increased, Liver function tests increased, Fracture, Bronchitis, Dyspnea

\* < 1%, post-marketing, and case reports: anaphylaxis, angioedema, bilirubin increased, CVA, cerebral ischemia, cerebral infarct, cutaneous vasculitis (including Henoch-Schönlein purpura), endometrial cancer, erythema multiforme, hepatitis, jaundice, joint pain, joint stiffness, liver inflammation, liver pain, liver swelling, myocardial ischemia, pulmonary embolus, retinal vein thrombosis; skin reactions (eg, blisters, lesions, ulcers); Stevens-Johnson syndrome, trigger finger, urticaria.

*Pregnancy and Lactation:* Pregnancy category X. Fetal toxicity was observed in animal studies. It is not known if anastrozole is excreted into breast milk.

### **Potential for Drug-Drug Interaction with Anastrozole:**

Anastrozole is a weak CYP3A4 inhibitor. Due to potential drug interactions, a complete patient medication list, including anastrozole, should be screened prior to initiation of anastrozole.

### **1.3.2 Benefits**

Women with advanced stage or recurrent endometrial cancer are difficult to cure with high rates of relapse and poor response to second line chemotherapy. Furthermore, there is a paucity of approved agents for relapsed or refractory endometrial cancer in the second line setting. The development of effective therapies for recurrent endometrial cancer represents an unmet clinical need. Using targeted hormonal treatment may present potential opportunities for improved treatment outcomes for these women. We hypothesize that onapristone with anastrozole will result in an improved overall response rate and improved 4 month progression free survival in patients with metastatic endometrial cancer. We also hypothesize that the combination will lead to improved quality of life for women with recurrent metastatic endometrial cancer.

## **2 Study Objectives**

### **2.1 Objectives**

The purpose of this study is to evaluate the activity and safety of a pure progesterone receptor (PR) antagonist, onapristone, with anastrozole to treat women with recurrent metastatic ER+/PR+ endometrial carcinoma. Our hypothesis is targeting the PR receptor with a pure PR antagonist will improve treatment outcomes..

#### **2.1.1 Co-Primary Endpoints**

- To evaluate the objective response rate (ORR) using RECIST 1.1 and
- To evaluate the 4-month progression free survival as a binary endpoint

### 2.1.2 Secondary

- To estimate the disease control rate (DCR)
- To describe duration of response (DOR)
- To evaluate the safety and tolerability
- To evaluate quality of life using the Edmonton Symptom Assessment questionnaire

### 2.1.3 Exploratory

- To characterize the ER and PR expression by IHC pre- and post-treatment

## 2.2 Endpoints/Outcome Measures

### 2.2.1 Primary

- Co-primary endpoints will be used:
  - Overall response rate as defined by the percentage of patients with tumor response (complete response or partial response) as defined by RECIST 1.1
  - 4-month Progression-Free-Survival (PFS) is defined as a binary endpoint, from first dose of onapristone and anastrozole to 4 months of therapy as “confirmed progression-free” or “not progression-free” (including cancer progression or censored subjects). We will use the date of first documented disease progression or recurrence, as assessed by using RECIST 1.1 criteria, or death due to any cause, whichever occurs first. Subjects who died without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress will be censored on the date of their last evaluable tumor assessment.

### 2.2.2 Secondary

- Disease control rate (DCR) defined as best overall response of CR, PR or SD lasting for  $\geq 24$  weeks, per RECIST 1.1
- Time to Response defined as time from randomization to first documented response (CR or PR) in months
- Duration of Response defined as time between the first date of documented response to progression or death due to endometrial cancer
- Safety and tolerability defined as type, frequency and severity of adverse events and laboratory abnormalities, per CTCAE v5.0
- Quality of life and pain scores is defined by the Edmonton Symptom Assessment System (ESAS) using nine subjective patient measures of well-being including pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being, shortness of breath. These will be rated by the patients during each visit (visits 1-6) and the change in values will correlate to an improvement in quality of life (a positive change will correlate to an improvement and a negative change will correlate to a worsening of pain).

### 2.2.3 Exploratory

- ER and PR expression assessed by immunohistochemistry (IHC) and represented as a percentage prior to trial initiation and at progression

## 3 Study Design

### 3.1 Characteristics

This is a multicenter, prospective phase II clinical trial. Patients with ER+/PR+ ( $\geq 1\%$  by IHC), recurrent, locally advanced, or metastatic endometrial cancer Patients will receive:

Onapristone ER 50 mg PO BID + anastrozole 1 mg PO QD until November 30, 2023, or disease progression, or an adverse event that requires patient to be removed from study. After discontinuation from study treatment, patients will be treated at the investigator's discretion as per standard of care.

Patients will be administered continuous dosing of both agents starting on Cycle 1 Day 1 in a 28-day cycle. There will be no breaks between dosing cycles. Subjects must not have had prior hormonal therapy  $>2$  months prior to study initiation, and must have ECOG status of 0-1. Patients will be treated until November 30th, 2023, or disease progression, unacceptable toxicity, or discontinuation from the study for any other reason.

H&P, vitals, lab studies, adverse events, and review of medications will be performed day 1 of each cycle. Imaging assessment (CT or MRI) will be performed every 8 weeks during first 4 months, and every 12 weeks thereafter. Additional imaging will be performed as clinically indicated.

### 3.2 Number of Participants

25 patients will be participating in this study.

### 3.3 Duration of Therapy

Patients are eligible to be on treatment with both agents until November 30<sup>th</sup>, 2023, disease progression, or an adverse event that requires patient to be removed from study.

### 3.4 Duration of Follow Up

- 3.5 If a patient is removed from the study for an event other than disease progression, they will be followed every 3 months for survival follow up. If patients are without disease progression on November 30th, 2023, they will be followed every 3 months for survival follow up until the time of first disease progression. **Study Timeline**

#### 3.5.1 Primary Completion

We anticipate accrual of 25 patients to the study over a 24 month time period. Patients will remain on study until disease progression or an adverse event that requires patient to be removed from study

### 3.5.2 Study Completion

We anticipate completion of the study in 36 months.

## 4 Study Enrollment and Withdrawal

### 4.1.1 Inclusion Criteria

Individuals must meet all of the following inclusion criteria in order to be eligible to participate in the study:

1. Age greater than or equal to 18 years old
2. Histologically confirmed diagnosis of endometrial cancer with ER and/or PR expression  $\geq 1\%$  by IHC on archival tissue taken within the prior 3 years or new biopsy if no archival tissue is available. IHC results do not have to be from Thomas Jefferson University. Standard of care testing for Next Generation Sequencing- If NGS results not available prior to enrollment, patient can still enroll onto study and have NGS testing ordered as SOC with archival tissue.
3. Patients are not required to be treated with platinum-based chemotherapy prior to going on trial
4. Treatment with up to 2 prior line of therapy allowed.
5. Measurable disease as defined by RECIST v.1.1. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension. Each lesion must be  $\geq 10\text{mm}$  when measured by CT or MRI. Lymph nodes must be  $\geq 15\text{mm}$  in short axis when measured by CT or MRI
6. Patients with the following histologic epithelial cell types are eligible:
  - a. Endometrioid adenocarcinoma
  - b. Serous adenocarcinoma
  - c. Undifferentiated carcinoma
  - d. Clear cell adenocarcinoma
  - e. Mixed epithelial carcinoma
  - f. Adenocarcinoma not otherwise specified (NOS)
  - g. Please note: patients with carcinosarcoma are ineligible for this trial.
7. ECOG Performance status 0-1.
8. Must have a life expectancy of at least 12 weeks as judged by the treating physician.
9. Females are only eligible for this study if they are postmenopausal. This is defined as meeting one of the following criteria:
  - a. S/p Total Abdominal Hysterectomy and Bilateral Salpingo-Oophorectomy
  - b. 12 consecutive months of amenorrhea in a woman over 55 in the absence of other biological or physiological causes
  - c. Documented serum follicle stimulating hormone (FSH) level less than 40 mIU/mL for women under the age of 55
10. Body weight  $>30\text{ kg}$
11. Adequate organ function:
  - a. Absolute neutrophil count  $1500/\mu\text{l}$  or more;

- b. Platelets 100,000/ $\mu$ l or more,
  - c. Hemoglobin 9 g/dl or more;
  - d. Bilirubin less than or equal to 1.5 x the upper limit of normal (except subjects with Gilbert syndrome, who can have total bilirubin <3 mg/dl);
  - e. Endocrine and targeted therapy protocols usually enroll patients with AST/ALT <2.5 x ULN in patients without underlying liver metastasis and <5.0 x ULN in patients with underlying liver metastasis.
  - f. GFR greater than or equal to 40 ml/min using the Cockcroft-Gault formula or measured creatinine clearance using 24 hours urine collection
  - g. International normalized ratio (INR) OR prothrombin time (PT) and activated partial thromboplastin time (aPTT)  $\leq 1.5 \times$  ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
- 12. All subjects must be able to comprehend and sign a written informed consent document.
  - 13. Resolution of all acute toxic effects of prior therapy to NCI CTCAE (Version 5.0) Grade  $\leq 1$ , with the exception of unresolved Grade 2 neuropathy and Grade 2 alopecia, which are allowed
  - 14. Patient has recovered from any prior radiotherapy
  - 15. Patients must be able to swallow tablets whole, without crushing
  - 16. Be able to read and speak English.

#### 4.1.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- 1. Concurrent or recent chemotherapy, radiotherapy, immunotherapy, or general anesthesia/major surgery **within 3 weeks**.
- 2. History of prior hormonal therapy (i.e., megestrol acetate, tamoxifen or aromatase inhibitors) for treatment cancer within the **past 2 months**. Other concurrent hormonal therapy will not be allowed on this trial.
- 3. Patient has a concurrent malignancy or history of invasive malignancy within 3 years of enrollment, with the exception of basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix that has completed curative therapy
- 4. If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.
- 5. Has received prior systemic anti-cancer therapy including investigational agents within 3 weeks prior to randomization.
- 6. Known brain metastasis which have not been treated or showed stability for  $\geq 6$  months
- 7. Proteinuria >1+ on urinalysis or >1 gm/24hr.
- 8. Known history of New York Heart Association stage 3 or 4 cardiac disease.
- 9. A pleural or pericardial effusion of greater than or equal to grade 3 severity
- 10. Women who are pregnant or nursing.
- 11. Has an active infection requiring systemic therapy.
- 12. Use of any prescription medication during the prior 28 days of first onapristone dosing that the investigator judges is likely to interfere with onapristone

activity; specifically strong inhibitors or inducers, or sensitive substrates of cytochrome P450 CYP3A4. Investigators should consult the following table of clinically-relevant products

<http://medicine.iupui.edu/CLINPHARM/ddis/clinical-table>.

13. Patients may not be on a concurrent clinical trial, unless approved by Investigator.

## 4.2 Gender/Minority/Pediatric Inclusion for Research

Endometrial cancer is a disease of women, and this protocol is directly aimed at female patients. Potential study subjects will be approached for participation in the trial regardless of race, ethnicity, socioeconomic status, sexual orientation, or minority identifier. Pediatric patients will be excluded from this protocol.

## 4.3 Strategies for Recruitment and Retention

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at participating centers from Medical Oncology or Gynecology Oncology. Investigators will screen the patient's medical records for suitable research study subjects and discuss the study and their potential for enrolling in the research study. Patients will be screened based on pathology, imaging studies, etc.

## 4.4 Participant Withdrawal

### 4.4.1 Reasons for Withdrawal

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may terminate a study participant's participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

Subjects **must** be withdrawn from the study for the following reasons:

- Further participation would be injurious to the subject's health or well-being, in the investigator's medical judgment.
- The subject is unable to reliably adhere to the study procedures.
- The subject exhibits extreme anxiety during the treatment.
- Consent is withdrawn.
- Staff members are unable to contact the subject or proxy to collect post-procedure information will count as withdrawal.

- Significantly progressive disease unless in the investigator's opinion, the subject would derive benefit from continued treatment.
- The study is terminated by Thomas Jefferson University
- The study is terminated by the local health authority or IRB.

A subject **may** be withdrawn from the study as follows:

- If, during the course of the study, a subject is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the subject should be withdrawn from the study.
- If a subject is noncompliant with study procedures or study drug administration in the opinion of the investigator, the sponsor should be consulted for instruction on handling the subject.
- The subject becomes pregnant.
- The subject demonstrates evidence of progressive disease as per RECIST v1.1

#### **4.4.2 Handling of Participant Withdrawals and Participant Discontinuation of Study Intervention**

Patients who are discontinued from the study prior to initiation of treatment will not be considered as evaluable for this study and will be replaced.

In the event that the decision is made to permanently discontinue the study drug, the subject will be withdrawn from the study and the end-of-treatment (EOT) visit should be conducted. Reasonable efforts should be made to have the subject return for a follow-up visit. The last date of the last dose of study drug will be recorded in the CRF, and the reason for subject withdrawal will be recorded.

#### **If a subject is withdrawn from the study:**

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the subject's medical record and in the CRF.
- The EOT or early termination visit should be performed.
- Subjects must be followed for safety until the time of the follow-up visit or until study drug-related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer.

#### **4.5 Premature Termination or Suspension of Study**

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Insufficient adherence to protocol requirements.
- Data that is not sufficiently complete and/or evaluable.
- Determination of futility.

## **5 Study Intervention**

### **5.1 Study Product**

Onapristone is a type 1 anti-progestin which prevents the PR from dimerizing (Allan et al., 1992) and does not result in ligand-induced phosphorylation of the PR (Beck et al., 1996; Clemm et al., 2000).

### **5.2 Study Product Description**

#### **5.2.1 Acquisition**

For this research study, onapristone will be supplied by Context Therapeutics to Thomas Jefferson University until November 30<sup>th</sup>, 2023. The drug will be obtained by the investigational drug pharmacy and will be given to the patient once eligibility has been established and consent is signed.

Anastrozole is a generic and affordable medication that is currently considered to be a reasonable second line option for patients with advanced or recurrent endometrial cancer, and therefore the medication will be commercially available and billed to the patient's insurance company.

#### **5.2.2 Formulation, Packaging, and Labeling**

### **Physical Properties**

Onapristone is a light yellow to green crystalline compound with a melting point of 155°C.

### **Chemical Properties**

Onapristone is a weak base with a pKa of 5.1. The logP is 4.03 and the logD is 3.97. Preliminary data from the active pharmaceutical ingredient (API) accelerated stability study shows no significant degradation after a storage period of eight weeks at 40°C/75% relative humidity. After irradiation with light according to International Conference on Harmonisation (ICH) guidelines the compound remained stable.

### **Onapristone Extended Release Tablets, 10 mg, 20 mg:**

Onapristone 10 mg and 20 mg coated tablets are an extended release solid dosage form (ER tablets) for oral administration. The 10mg strength is a smaller salmon pink coated oval biconvex tablets. The 20mg strength is a 14 x 7.8mm yellow coated oval biconvex tablet. The quantitative composition of the ER tablets is provided in Table 4. The drug product is packaged in a 60 mL round HDPE bottle with a child-resistant polypropylene (PP) cap. Each bottle provided by Context Therapeutics to IDS is labeled with FDA required information. Each bottle will be overlabeled with a pharmacy dispensing label at time of dispensing.

The quantitative composition of the extended-release tablets is a common granulation and is presented in Table 4.

**Table 4: Quantitative Composition of Onapristone Extended-Release Tablets**

| Table 1: Qualitative Composition of Onapristone Extended Release Tablets |                                            |                        |       |                        |
|--------------------------------------------------------------------------|--------------------------------------------|------------------------|-------|------------------------|
| Component                                                                | Reference to quality standard              | Amount per tablet (mg) |       | Function               |
|                                                                          |                                            | 10 mg                  | 20 mg |                        |
| Tablet Core-                                                             |                                            |                        |       |                        |
| Onapristone <sup>1</sup>                                                 | Refer to <a href="#">Section 3.2.S.4.1</a> | 10.0                   | 20.0  | Active                 |
| Lactose monohydrate                                                      | USP, Ph. Eur., JP                          | 41.0                   | 82.0  | Filler                 |
| Microcrystalline cellulose                                               | USP, Ph. Eur., JP                          | 41.0                   | 82.0  | Filler / binder        |
| Pregelatinized starch                                                    | USP, Ph. Eur.                              | 40.0                   | 80.0  | Filler / binder        |
| Hydroxypropyl methylcellulose                                            | USP, Ph. Eur., JP                          | 65.0                   | 130.0 | modified release agent |
| Colloidal silicon dioxide                                                | USP, Ph. Eur., JP                          | 1.0                    | 2.0   | Glidant                |
| Magnesium stearate                                                       | USP, Ph. Eur., JP                          | 2.0                    | 4.0   | Lubricant              |
| Tablet weight (mg)                                                       |                                            | 200.0                  | 400.0 |                        |
| Tablet Coating-                                                          |                                            |                        |       |                        |
| Opadry II <sup>2,3,4</sup>                                               | [See Section 3.2.P.4.1.1]                  | 7.53                   | 15.04 | Color film coating     |
| Purified water <sup>5</sup>                                              | USP, Ph. Eur.                              | N/A                    | N/A   | Processing aid         |
| Tablet weight (mg)                                                       |                                            | 207.5                  | 415.0 |                        |

<sup>1</sup> Onapristone powder is adjusted for purity

<sup>2</sup> Coating suspension prepared with a 15% concentration of dry material (w/w).

<sup>3</sup> Opadry II 85F140054 Pink on 10mg ER tablet

<sup>4</sup> Opadry II 85F12374 Yellow on 20mg ER tablet

<sup>5</sup> Purified water removed during manufacturing process

The extended-release tablet is expected to be used in planned safety and efficacy studies.

### 5.2.3 Product Storage and Stability

The tablets can be stored in ambient conditions, at controlled room temperature (15-30°C).

Each lot of onapristone extended release tablets are monitored on stability at  $40 \pm 2^\circ\text{C}/75 \pm 5\%$  for 6 months and at  $25 \pm 2^\circ\text{C}/60 \pm 5\%$  for at least 3 years or for the duration of use in the clinic, whichever is longer. Based on product stability of coated and uncoated onapristone ER tablets, the shelf life for the coated extended release tablets is currently set at 24 months and may be extended.

### 5.3 Dosage, Preparation, and Administration

Onapristone will be taken orally as outlined in the treatment schema. Patients will be provided with a diary in which to record their intake of study drug. However, the actual number of tablets taken by the patient must be calculated from patient diaries and the number of tablets dispensed and returned.

Onapristone will be administered as a flat-fixed dose (50 mg twice daily), and not by body weight or body surface area. For this study, patients will be taking two 20 mg tablet and one 10 mg tablet. Patients will take one dose (which is three tablets for DL1) in the morning and one dose in the evening. We will emphasize importance of consistently taking the pills at the same time every day with food and water. Patients should not take an extra dose if a dose is missed. Patients will be instructed to return unused study drug to the site at discontinuation or completion of treatment. The site personnel must ensure that the appropriate dose of each study drug is administered and that the drug accountability is performed. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded.

Anastrozole: Anastrozole will be taken orally as outlined in the treatment schema. Patients will be provided with a diary in which to record their intake of study drug. However, the actual number of tablets taken by the patient must be calculated from patient diaries and the number of tablets dispensed and returned.

Anastrozole will be administered as a flat-fixed dose (1 mg daily), and not by body weight or body surface area. For this study, the 1 mg strength tablets will be used to achieve the 1 mg dose levels. Patients will take the one dose in the morning. We will emphasize importance of consistently taking the pills at the same time every day with food and water. Patients should not take an extra dose if a dose is missed. Patients will be instructed to return unused study drug to the site at discontinuation or completion of treatment. The site personnel must ensure that the appropriate dose of each study drug is administered and that the drug accountability is performed. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded.

### 5.4 Dose Modifications and Dosing Delays

#### Overview of Dose Adjustments for Onapristone ER Toxicity

Any dose modification of onapristone ER requires consultation with the study PI.

- If Grade 1 or 2 toxicities occur, give supportive care per institutional guidelines. No onapristone ER dose reduction should occur unless discussed with study PI.

- If  $\geq$  Grade 3 toxicities occur that are considered potentially related to onapristone ER, including headache, nausea, vomiting, LFT elevation or diarrhea, hold onapristone ER until the toxicity resolves to  $\leq$  Grade 1 (unless was Grade 2 at baseline, then when returns to baseline). If onapristone ER is held for LFT elevation, then LFT levels should be checked weekly until  $\leq$  Grade 1 or baseline, and then onapristone ER resumed with dose reduction as per table below.
- If onapristone ER is held for  $\leq 28$  days it may be restarted at the same or a reduced dose at the discretion of the treating physician (except in the case of LFT elevation, which requires dose reduction).
- If onapristone ER is held for  $>28$  days the patient should be removed from study treatment. Anastrozole can be continued but the patient will be discontinued from the trial.
- Onapristone dose reductions will occur as per the table below:

|                          |                         |
|--------------------------|-------------------------|
| <b>Starting Dose</b>     | <b>50 mg PO BID</b>     |
| <b>Dose Reduction #1</b> | 30 mg PO BID            |
| <b>Dose Reduction #2</b> | 10 mg PO BID            |
| <b>Dose Reduction #3</b> | Permanently Discontinue |

### Overview of Criteria for Holding Anastrozole for Toxicity

There will be no dose modification of anastrozole during the study. If toxicities are thought to be related to anastrozole, anastrozole will be held completely. Holding anastrozole requires consultation with the Study Primary Investigators (Dr. Buchanan).

- If Grade 1 or 2 toxicities occur, give supportive care per institutional guidelines. Anastrozole should not be held unless discussed with study PI.
- If  $\geq$  Grade 3 toxicities occur that are considered potentially related to anastrozole, and not onapristone ER, including arthralgias, vasomotor symptoms, headache, nausea, vomiting, hold anastrozole until the toxicity resolves to  $\leq$  Grade 1 (unless was Grade 2 at baseline, then when returns to baseline) and discussion with the study Primary Investigator
- If anastrozole is held for  $\leq 28$  days it may be restarted at the same dose at the discretion of the treating physician per discussion with the Primary Investigator
- If anastrozole is held for  $>28$  days the patient should be removed from study treatment even if a patient is tolerating Onapristone alone.

### 5.5 Study Product Accountability

Clinical drug supply must be accounted for and patients will be asked to return all unused study drug and packaging on a regular basis, at the end of the study, or at the time of study drug discontinuation.

Compliance should be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver. Records of study medication used, dosages administered, and intervals between visits and the completion of the study should be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

At the conclusion of the study, and, as appropriate during the course of the study, the study drug will be destroyed on site. All packaging, drug labels, and a copy of the completed drug accountability ledger to Context Therapeutics.

#### **5.6 Assessing Participant Compliance with Study Product Administration**

In order to assess for compliance with study product administration, patients will maintain a pill diary during study administration and study staff will perform a pill count at the end of the four-week treatment period.

5.7. There are no dietary restrictions with onapristone or anastrozole.

#### **5.7 Concomitant Medications/Treatments**

The use of any natural/herbal products or other traditional remedies should be discouraged. Use of these products, as well as 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 enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Medications that may **NOT** be administered:

**Table 4 Prohibited medications**

| <b>Prohibited medication/class of drug:</b>                                                                                                                          |                                                                                                       |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Anticancer therapy:<br>Chemotherapy<br>Immunotherapy<br>Hormonal replacement therapy<br>Radiotherapy (except palliative)<br>Biological therapy<br>Other novel agents | Not permitted while the patient is receiving study medication                                         |
| Live virus vaccines<br>Live bacterial vaccines                                                                                                                       | Not permitted while the patient is receiving study medication and during the 30 day follow up period. |

**Table 5 Restricted concomitant medications**

| <b>Medication/class of drug:</b>                                                                                                                                                                                                                                    | <b>Usage (including limits for duration permitted and special situations in which it's allowed ):</b> |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Strong CYP3A inhibitors:<br>itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir<br><br>Moderate CYP3A inhibitors:<br>ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil | Strong or moderate CYP3A inhibitors should not be taken with <i>onapristone</i> .                     |
| Strong inducers:<br>phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort<br><br>Moderate CYP3A inducers:<br>bosentan, efavirenz and modafinil                                                   | Strong or moderate CYP3A inducers should not be taken with <i>onapristone</i> .                       |

## Anticoagulant therapy

Patients who are taking warfarin may participate in this trial; however, it is recommended that international normalized ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin and low molecular weight heparin are permitted.

## 6 Study Schedule

### 6.1 Study Schedule

| Procedures                            |                                                        | Screening<br>(Day -30 to -1) |  | Study Visit (3,8)<br>Cycle 1, D1 | Study Visit (3)<br>Cycle 2, D1 | Study Visit (3)<br>Cycle 3 D1 | Study Visit (3)<br>Cycle 4 D1 | Study Visit (3)<br>Cycle 5 D1 | Study Visit (3)<br>Cycle 6 D1 and each<br>additional cycle | End of Treatment<br>visit (5) | Long Term/Survival<br>Follow-up |
|---------------------------------------|--------------------------------------------------------|------------------------------|--|----------------------------------|--------------------------------|-------------------------------|-------------------------------|-------------------------------|------------------------------------------------------------|-------------------------------|---------------------------------|
| Sign Consent Form                     |                                                        | X                            |  |                                  |                                |                               |                               |                               |                                                            |                               |                                 |
| Assessment of Eligibility<br>Criteria |                                                        | X                            |  |                                  |                                |                               |                               |                               |                                                            |                               |                                 |
| Review of Medical History             |                                                        | X                            |  |                                  |                                |                               |                               |                               |                                                            |                               |                                 |
| Baseline EKG (2)                      |                                                        | X                            |  |                                  |                                |                               |                               |                               |                                                            |                               |                                 |
| Review of Concomitant<br>Medications  |                                                        | X                            |  | X                                | X                              | X                             | X                             | X                             | X                                                          | X                             |                                 |
| Study<br>Interventio<br>n             | Onapristone<br>and<br>Anastrozole<br>1 mg Daily<br>(7) |                              |  | X                                | X                              | X                             | X                             | X                             | X                                                          |                               |                                 |
| Physician<br>Assessment               | Vitals (1)                                             | X                            |  | X                                | X                              | X                             | X                             | X                             | X                                                          | X                             |                                 |
|                                       | Physical<br>Examination                                | X                            |  | X                                | X                              | X                             | X                             | X                             | X                                                          | X                             |                                 |
| Edmonton's Symptom<br>Assessment      |                                                        | X                            |  | X                                | X                              | X                             | X                             | X                             | X                                                          | X                             |                                 |
| Assessment of Adverse<br>Events       |                                                        | X                            |  | X                                | X                              | X                             | X                             | X                             | X                                                          | X                             |                                 |
| Laboratory<br>Studies                 | Hematology                                             | X                            |  | X                                | X                              | X                             | X                             | X                             | X                                                          | X                             |                                 |
|                                       | Chemistry<br>(including<br>LFTs)                       | X                            |  | X                                | X                              | X                             | X                             | X                             | X                                                          | X                             |                                 |
|                                       | Coagulation<br>(10)                                    | X                            |  | X                                | X                              | X                             | X                             | X                             | X                                                          | X                             |                                 |
|                                       | Urine<br>Analysis                                      | X                            |  |                                  |                                |                               |                               |                               |                                                            |                               |                                 |

| Procedures                                                         |                       | Screening<br>(Day -30 to -1) |  | Study Visit (3,8)<br>Cycle 1, D1 | Study Visit (3)<br>Cycle 2, D1 | Study Visit (3)<br>Cycle 3 D1 | Study Visit (3)<br>Cycle 4 D1 | Study Visit (3)<br>Cycle 5 D1 | Study Visit (3)<br>Cycle 6 D1 and each<br>additional cycle | End of Treatment<br>visit (5) | Long Term/Survival<br>Follow-up |
|--------------------------------------------------------------------|-----------------------|------------------------------|--|----------------------------------|--------------------------------|-------------------------------|-------------------------------|-------------------------------|------------------------------------------------------------|-------------------------------|---------------------------------|
| Imaging                                                            | CT scan or<br>MRI (4) | X                            |  |                                  |                                | X                             |                               | X                             | X                                                          |                               |                                 |
| Imaging                                                            | DEXA                  | X                            |  |                                  |                                |                               |                               |                               |                                                            |                               |                                 |
| Tumor Biopsy or archival<br>tissue (with IHC and NGS)<br>(6 and 9) |                       | X                            |  |                                  |                                |                               |                               |                               |                                                            |                               |                                 |
| Follow-up                                                          |                       |                              |  |                                  |                                |                               |                               |                               |                                                            |                               | X (11)                          |

- 1: Vital signs: blood pressure, heart rate, respiratory rate, temperature and weight. Height need only be taken on Cycle 1, Day 1.
- 2: Hypokalemia should be corrected prior to EKG collection
- 3: All visits have a  $\pm 5$  day window unless otherwise noted
- 4: Radiographic tumor assessment of abdomen and pelvis may be performed using CT or MRI. Chest imaging should occur by CT. There is a  $\pm 7$  day window for completion of interval tumor assessments by imaging. Radiographic tumor assessments will occur every 8 weeks during first 4 months, and every 12 weeks thereafter until disease progression.
- 5: End of Study Treatment Visit should happen within 30 days of last dose of study drug.
- 6: Standard of care testing for Next Generation Sequencing. If NGS results not available prior to enrollment, patient can still enroll onto study and have NGS testing ordered as SOC with archival tissue.
- 7: Pill diary and study drug should be given to patient.
- 8: For C1D1 labs- if the screening labs have been done within 14 days of C1D1, then they need not be repeated.
- 9: ER/PR status can be obtained from the archival data
10. Only patients who are taking warfarin must have international normalized ratio (INR) monitored at least once per week for the first month, then monthly if the INR is stable
11. If a patient is removed from the study for an event other than disease progression, survival follow up will occur every 3 months ( $\pm 21$  days). If patients are without disease progression on November 30th, 2023, they will be followed every 3 months ( $\pm 21$  days) for survival follow up until the time of first disease progression. Survival follow up may occur by phone call or chart review.

## 6.1 Pretreatment Period/Pre-Screening

The screening phase is the interval between the signing of the ICF and the day the subject begins study treatment (Cycle 1). Informed consent must be obtained before performing any study-specific procedures.

1. Results from the screening visit evaluations will be reviewed to confirm subject eligibility before the administration of study drug. Tests with results that fail eligibility requirements may be repeated once during the screening phase if the investigator believes the results to be in error. Additionally, a subject who fails screening may repeat the screening process 1 time if the investigator believes there has been a change in eligibility status (e.g., following recovery from an infection). After review of all screening information, an entry will be made in the Screening & Enrollment Log for all participants who consent to be in the study; whether or not they qualify after the screening procedures.
2. If any participant is determined to meet preliminary eligibility criteria, and expresses willingness to continue with the study, she will proceed. Detailed instructions, study-specific procedures and study calendar will again be explained to qualified participant.

### Screening Visit (Day -30 to -1)

- Obtain and document consent from potential participant on screening consent form.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Perform medical physical examination to determine eligibility.
- Collect blood and urine samples for laboratory studies
- EKG assessment
- Vitals including blood pressure, heart rate, temperature, height and weight
- Edmonton's Symptom Assessment
- Assessment of Adverse Events
- DEXA Imaging
- CT chest and CT or MRI of abdomen and Pelvis
- Next Generation Sequencing or plan to submit standard of care archival tissue for Next Generation Sequencing with any commercial company such as Foundation Medicine or Caris

### Study Visit Cycle 1, day 1

- Physical exam Vitals including blood pressure, heart rate, respiratory rate, temperature, height, and weight

- Edmonton's Symptom Assessment
- Assessment of Adverse Events
- Laboratory Studies
- Review of Concomitant Medications
- Collect blood test if necessary.
- Dispense onapristone, and pill diary

## 6.2 Treatment Period

The Treatment Phase, and enrollment into the study, will begin with the initial dose of onapristone + anastrozole, on Day 1 of Cycle 1.

Visits will occur at the time points noted in study table in **Section 6**. Each cycle is 28 days of therapy. For all cycles a window of  $\pm 5$  days will be permitted. Patients may be on treatment until November 30<sup>th</sup>, 2023, disease progression or an adverse event that requires patient to be removed from study.

If a subject has to hold dosing in a given cycle, dosing maybe resumed after reassessment by the physician. Dosing cycles will not be postponed but will occur every 28 days.

### Every 28 day cycles $\pm 5$

- Record adverse events as reported by participant or observed by investigator.
- physical examination.
- Vitals including blood pressure, heart rate, respiratory rate, temperature, and weight
- Review of Concomitant Medications
- Edmonton's Symptom Assessment
- Collect blood laboratory studies
- Radiographic tumor assessments will occur every 8 weeks during first 4 months, and every 12 weeks thereafter until disease progression
- Collect and dispense onapristone, and pill diary
- Record participant's compliance with the intervention.

## 6.3 End of Treatment Study Procedures

If a decision is made that the subject will permanently discontinue study drug, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT page in the CRF.

### **End of treatment visit (within 30 days of treatment discontinuation)**

- Record adverse events as reported by participant or observed by investigator.
- physical examination
- Vitals including blood pressure, heart rate, respiratory rate, temperature, and weight
- Review of Concomitant Medications
- Edmonton's Symptom Assessment
- laboratory studies
- Collect onapristone, and pill diary
- Record participant's compliance with intervention.
- Provide final instructions to participant

### **6.4 Long Term/Survival Follow-up**

The follow-up phase is the interval between the last dose and the scheduled follow-up visit. Survival follow up will occur every 3 months (+/-21 days) after end of treatment visit and may occur by phone. Adverse events and SAEs must be reported for at least 28 days after the last dose of study drug, the date of the follow-up visit, or Ongoing AEs at the time of end of treatment should be followed until study drug-related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. .

### **6.5 Withdrawal Visit/Discontinuation of Therapy**

In the absence of treatment delays because of AEs, treatment will continue until one of the following criteria applies:

- subject decides to withdraw from the study
- radiographic disease progression
- symptomatic disease progression at any time
- objective clinical disease progression
- inter-current illness that prevents further administration of treatment
- unacceptable AE(s) that may or may not be directly related to treatment but that, in the judgment of the treating physician, makes it dangerous for the subject to be retreated
- general or specific changes in the patient's condition that render the patient unacceptable for further treatment, in the judgment of the investigator

Because an excessive rate of withdrawals can render the study uninteruptable, unnecessary withdrawal of subjects should be avoided. When a subject discontinues treatment early, the investigator should make every effort to contact the subject and to perform a final evaluation. The reason(s) for withdrawal should be recorded.

## **7 Study Procedures and Evaluations**

## **7.1 Study Procedures/Evaluations**

Please reference Section 6 for table of study assessments.

## **7.2 Laboratory Procedures/Evaluations**

### **7.2.1 Clinical Laboratory Evaluations**

- CBC with differential, CMP including LFTs, coagulation studies (INR)

## **8 Evaluation of Safety**

### **8.1 Specification of Safety Parameters**

#### **8.1.1 Unanticipated Problems**

Unanticipated problems (UAPs) include, in general, any incident, experience, or outcome that meets the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

UAPs are considered to pose risk to participants or others when they suggest that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

#### **8.1.2 Adverse Events**

An adverse event is any untoward or unfavorable medical occurrence in a human participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research.

#### **8.1.3 Serious Adverse Events**

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the participant at immediate risk of death from the event as it occurred)
- Is disabling or incapacitating
- Results in inpatient hospitalization or prolongation of existing hospitalization

- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the participant or may require intervention to prevent one of the outcomes listed in this definition.

## 8.2 Safety Assessment and Follow-Up

Adverse events and serious adverse events will be followed starting after first administration of study medication until 28 days after the last administration of study medication. Ongoing AEs at the time of end of treatment should be followed until study drug-related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. At each study visit, the investigator (or designee) will inquire about the occurrence of AE/SAEs since the last visit.

## 8.3 Recording Adverse Events

The following subsections detail what information must be documented for each adverse event occurring during the time period specified in Section 8.2 Safety Assessment and Follow-Up.

### 8.3.1 Relationship to Study Intervention

The relationship to study intervention or study participation must be assessed and documented for all adverse events. Evaluation of relatedness must consider etiologies such as natural history of the underlying disease, concurrent illness, concomitant therapy, study-related procedures, accidents, and other external factors.

The following guidelines are used to assess relationship of an event to study intervention:

1. Related (Possible, Probable, Definite)
  - a. The event is known to occur with the study intervention.
  - b. There is a temporal relationship between the intervention and event onset.
  - c. The event abates when the intervention is discontinued.
  - d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
  - a. There is no temporal relationship between the intervention and event onset.
  - b. An alternate etiology has been established.

### 8.3.2 Expectedness

The PI is responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the

risk information previously described for the intervention. Risk information to assess expectedness can be obtained from preclinical studies, the investigator's brochure, published medical literature, the protocol, or the informed consent document.

### 8.3.3 Severity of Event

Adverse events will be graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

### 8.3.4 Intervention

Any intervention implemented to treat the adverse event must be documented for all adverse events.

## 8.4 Safety Reporting

### 8.4.1 Reporting to IRB.

#### 8.4.1.1 *Unanticipated Problems*

All incidents or events that meet criteria for unanticipated problems (UAPs) as defined in Section 8.1.1 Unanticipated Problems require the creation and completion of an unanticipated problem report form (OHR-20).

UAPs that pose risk to participants or others, and that are not AEs, will be submitted to the IRB on an OHR-20 form via the eazUP system within 5 working days of the investigator becoming aware of the event.

UAPs that do not pose risk to participants or others will be submitted to the IRB at the next continuing review.

##### 8.4.1.1.1 **Affiliate Site Unanticipated Problems Reporting**

Each affiliate site must submit the unanticipated problem report (OHR-20) for incidents occurring at their site.

#### 8.4.1.2 *Adverse Events*

Grade 1 AEs will be reported to the IRB at continuing review.

Grade 2 AEs will be reported to the IRB at the time of continuing review.

#### 8.4.1.3 *Serious Adverse Events*

SAEs will be reported to the IRB on OHR-10 forms via the electronic reporting system (eSAEy) according to the required time frames described below.

Grade 3-4 AEs that are unexpected and deemed to be at least possibly related to the study will be reported to the IRB within 2 working days of knowledge of the event.

Grade 3-4 SAEs that are deemed unrelated to the study will be reported to the IRB within 5 working days.

Grade 5 AEs will be reported to the IRB within one working day of knowledge of the event.

All SAEs will be submitted to the IRB at continuing review, including those that were reported previously.

Each affiliate site must submit the OHR-10 for SAEs occurring at their site.

#### **8.4.2 Reporting to SKCC DSMC**

All AEs and SAEs, safety and toxicity data, and any corrective actions will be submitted to the DSMC per the frequency described in the SKCC DSMP. The report to the SKCC DSMC will also include any unanticipated problems that in the opinion of the PI should be reported to the DSMC.

The affiliate site is required to provide copies of any Unanticipated Problems, protocol deviations, and AE logs to the TJU Study Site Contact for submission to the DSMC.

For expedited reporting requirements, see table below:

DSMC AE/SAE Reporting Requirements

|                            | Grade 1                                                  | Grade 2                                                  |                                                          | Grade 3                    |                                                          |                            |                                                          | Grades 4 and 5                                                       |
|----------------------------|----------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------|----------------------------|----------------------------------------------------------|----------------------------|----------------------------------------------------------|----------------------------------------------------------------------|
|                            | Unexpected and Expected                                  | Unexpected                                               | Expected                                                 | Unexpected                 |                                                          | Expected                   |                                                          | Unexpected and Expected                                              |
|                            |                                                          |                                                          |                                                          | With Hospitalization       | Without Hospitalization                                  | With Hospitalization       | Without Hospitalization                                  |                                                                      |
| Unrelated Unlikely         | Reviewed at Quarterly DSMC Meeting and IRB Annual Review | Reviewed at Quarterly DSMC Meeting and IRB Annual Review | Reviewed at Quarterly DSMC Meeting and IRB Annual Review | 5 Working Days             | Reviewed at Quarterly DSMC Meeting and IRB Annual Review | 5 Working Days             | Reviewed at Quarterly DSMC Meeting and IRB Annual Review | Phase I - 48 Hours<br>(Death: 24 Hours)<br>Phase II - 5 working days |
| Possible Probably Definite | Reviewed at Quarterly DSMC Meeting and IRB Annual Review | Reviewed at Quarterly DSMC Meeting and IRB Annual Review | Reviewed at Quarterly DSMC Meeting and IRB Annual Review | 48 Hours (Death: 24 Hours) | Phase I - 48 Hours<br>Phase II - 5 working days          | 48 Hours (Death: 24 Hours) | Reviewed at Quarterly DSMC Meeting and IRB Annual Review | Phase I and Phase II - 48 Hours<br>(Death: 24 Hours)                 |

#### 8.4.3 Reporting to Funding Sponsor

SAEs, whether related or not related to study drug, and pregnancies must be reported to Context Therapeutics within 24 hours. SAEs must be recorded on Context Therapeutics or an approved form. Women of child bearing potential are excluded from this study, but in the unexpected occurrence of pregnancy, this must be reported on a Pregnancy Surveillance Form. The TJU Study Site Contact is responsible for submitting SAEs to the funder that occur at the affiliate site. The affiliate site will provide the completed SAE form to the TJU Study Site Contact for reporting purposes.

SAE Email Address: [clinicaltrials@contexttherapeutics.com](mailto:clinicaltrials@contexttherapeutics.com)

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to Context Therapeutics (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

Site specific forms will be requested for review.

#### 8.4.4 Reporting to FDA

For studies conducted under an Investigator IND in the US, any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible and no later than 7 days (for a death or life-threatening event) or 15 days (for all other SAEs) after the investigator's or institution's initial receipt of the information. CONTEXT Pharmaceuticals will be provided with a simultaneous copy of all adverse events filed with the FDA. Thomas Jefferson University will submit SAE reports for all sites to the FDA. The TJU Study Site Contact is responsible for submitting SAEs to the funder that occur at the affiliate site. The affiliate site will provide the completed SAE form to the TJU Study Site Contact for reporting purposes.

SAEs should be reported on MedWatch Form 3500A, which can be accessed at: <http://www.accessdata.fda.gov/scripts/medwatch/>

MedWatch SAE forms should be sent to the FDA at:

MEDWATCH  
5600 Fishers Lane  
Rockville, MD 20852-9787  
Fax: 1-800-FDA-0178 (1-800-332-0178)  
<http://www.accessdata.fda.gov/scripts/medwatch/>

- An SAE report should be completed for any event where doubt exists regarding its seriousness.
- For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection in the protocol.

- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
- If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
- If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to CONTEXT Pharmaceuticals using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization. All SAEs should be followed to resolution or stabilization.

#### **8.4.5 Reporting of Pregnancy**

Pregnancy tests on blood or urine samples will be performed for women of childbearing potential within 30 days prior to the start of study treatment, on Day 1 of the study prior to commencing treatment, at the time points shown in Section 6 during study treatment and at the 30 day follow up visit. Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible/must be discontinued from study treatment immediately. Details of the pregnancy tests must be recorded in the patient's medical records.

#### **8.5 Halting Rules**

Adverse events and laboratory data from this trial will be assessed by the lead site on an ongoing basis. At least quarterly, data from the clinical database will be reviewed by the Primary Investigator. The results of this review will be shared with all investigators either in writing or as part of a teleconference. Serious adverse events will be reviewed as they are reported to the lead site/sponsor, and the medical monitor will make an assessment regarding the safety of continuing or modifying the study.

### **9 Study Oversight**

In addition to the PI's responsibility for oversight, study oversight will be under the direction of the SKCC's Data and Safety Monitoring Committee (DSMC). The SKCC DSMC operates in compliance with a Data and Safety Monitoring Plan (DSMP) that is approved by the NCI.

### **10 Clinical Site Monitoring and Auditing**

Clinical site monitoring and auditing is conducted to ensure that the rights of human participants are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring and auditing for this study will be performed in accordance with the SKCC's Data and Safety Monitoring Plan (DSMP) developed by the SKCC Data and Safety Monitoring Committee (DSMC). The DSMP specifies the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of participant data to be reviewed), and the distribution of monitoring reports. Some monitoring activities may be performed remotely, while others will take place at the study site(s). Appropriate staff will

conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the SKCC DSMP.

## **11 Statistical Considerations**

### **11.1 Study Hypotheses**

We hypothesize that the rate of objective response in our patient will be higher than the historical rate of 9-15% in historical control, and our rate of survival at 4-month will be higher than the historical 4-month survival rate of 25%.

### **11.2 Analysis Plans**

This is a single arm study that compares both the ORR and 4-month PFS rate for patients in our study to the historical ORR of 15% and 4-month PFS rate of 25%, using two-sided exact test of proportions at 5% significance level.

### **11.3 Interim Analyses and Stopping Rules**

#### **11.3.1 Safety Review**

A safety analysis for toxicity will be performed after the first eight patients are enrolled on the trial. Any grade 3 or 4 toxicities will be reviewed carefully.

#### **11.3.2 Efficacy Review**

Any subject who meets criteria and received at least one week of treatment with onapristone and anastrozole will be included in the efficacy review.

### **11.4 Sample Size Considerations**

Twenty-five (25) patients will achieve 86.9% power to detect a difference in the objective response rate of 40% vs. the historical control of 15% (null considered as constant), using two-sided exact test at 5% significance level. This effect size corresponds to observing 10 vs. 4 patients out of 25 patients with objective response. This sample size will also achieve 80.5% power to detect a difference in the 4-month progression-free-survival rate of 52% vs. the historical control of 25% (null considered as constant), using two-sided exact test at 5% significance level. This effect size corresponds to observing 13 vs. 6 patients being progression-free at 4-month out of 25 patients.

#### **11.4.1 Replacement Policy**

We will not allow for replacement for any patient who comes off trial due to toxicity or progression. Patients who discontinued from the study prior to initiation of treatment will not be considered as evaluable for this study and will be replaced.

#### **11.4.2 Accrual Estimates**

We hope to accrue ten to twelve patients per year to this trial.

## **12 Source Documents and Access to Source Data/Documents**

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, and regulatory and institutional requirements for the protection of confidentiality of participant information. Study staff will permit authorized representatives of SKCC and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

## **13 Quality Control and Quality Assurance**

The investigator will allocate adequate time for monitoring activities. The Investigator will also ensure that the medical monitor or other compliance or quality assurance reviewer is given access to all of the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

## **14 Ethics/Protection of Human Participants**

### **14.1 Ethical Standard**

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

### **14.2 Institutional Review Board**

The protocol, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

### **14.3 Informed Consent Process**

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the participant. Consent forms will be IRB-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study. The consent process will be documented in the clinical or research record.

#### **14.4 Participant Confidentiality**

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any study information relating to participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study participants. The clinical study site will permit access to such records.

### **15 Data Handling and Record Keeping**

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study participants, including accurate case report forms (CRFs), and source documentation.

#### **15.1 Data Management Responsibilities**

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

#### **15.2 Data Capture Methods**

Data will be captured in an electronic database (RedCap) which will be kept behind a password protected firewall database. Only the Principal Investigator and the research team members will have access to the data.

##### **15.2.1 Affiliate Site Data Management Plan**

This trial will be available at Jefferson New Jersey and Abington. We will ask clinical trial staff at each facility to provide assistance with data management. Dr. Buchanan will oversee the operations in all three campuses. We plan to monitor all data and also have monthly conference calls to assist co-primary investigators with the management of toxicities associated with each drug.

#### **15.3 Types of Data**

Clinical data that will be collected include patient history and physical examination data, safety, laboratory studies, pathology studies, treatment, diagnostic imaging, and immunohistochemistry as determined in the laboratory.

## **15.4 Study Records Retention**

Study records will be maintained for at least three years from the date that the grant federal financial report (FFR) is submitted to the NIH.

Study documents must be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

## **15.5 Protocol Deviations**

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedures requirements. The noncompliance may be on the part of the participant, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

All deviations from the protocol must be addressed in study participant source documents and promptly reported to the IRB and other regulatory bodies according to their requirements.

## **16 Study Finances**

### **16.1 Funding Source**

We currently have pharmaceutical support for this clinical trial, as well as access to extended release onapristone (Apiristor ER) tablets as provided by Context Therapeutics until November 30<sup>th</sup>, 2023.

Anastrozole is a generic and affordable medication that is currently considered to be a reasonable second line option for patients with advanced or recurrent endometrial cancer, and therefore this medication will likely be covered by the participant's insurance.

### **16.2 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 a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Jefferson University Investigators will follow the TJU Conflicts of Interest Policy for Employees (107.03).

### **16.3 Participant Stipends or Payments**

There will be no participant stipends or payments.

## 17 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human participants to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801 mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials:"

Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation;

Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.

NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

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## **SUPPLEMENTAL MATERIALS**

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

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## Appendices

The following documents are officially affiliated with the protocol and will be submitted to the IRB as a part of the protocol. As such, changes to these items require a protocol amendment.

Appendix A: Edmonton Symptom Assessment

Appendix B: RECIST 1.1

Appendix C: Pill Diary

## Appendix A: Edmonton Symptom Assessment

Edmonton Symptom Assessment System:  
Numerical Scale  
Regional Palliative Care Program

Please circle the number that best describes:

|                           |   |   |   |   |   |   |   |   |   |   |    |                                     |
|---------------------------|---|---|---|---|---|---|---|---|---|---|----|-------------------------------------|
| No pain                   | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible pain                 |
| Not tired                 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible tiredness            |
| Not nauseated             | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible nausea               |
| Not depressed             | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible depression           |
| Not anxious               | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible anxiety              |
| Not drowsy                | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible drowsiness           |
| Best appetite             | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible appetite             |
| Best feeling of wellbeing | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible feeling of wellbeing |
| No shortness of breath    | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible shortness of breath  |
| Other problem             | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |                                     |

Patient's Name \_\_\_\_\_

Date \_\_\_\_\_ Time \_\_\_\_\_

Complete by (check one)

☐ Patient

☐ Caregiver

## Appendix B: RECIST 1.1

As per Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-247

### ***Assessment and Decision at RECIST 1.1 Progression***

In participants who show evidence of radiological PD by RECIST 1.1 the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management (see Table 5 and Figures 1 and 3). This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed clinically unstable should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment. I

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to  $\geq 20\%$  and  $\geq 5$  mm from nadir
  - Please note: the iRECIST publication uses the terminology “sum of measurements”, but “sum of diameters” will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

## Appendix C: Pill Diary

Patient Initials: \_\_\_\_\_

Cycle # \_\_\_\_\_

Patient Study Number: \_\_\_\_\_

| Onapristone + Anastrozole Pill Diary                                                                                                                             |      |      |      |                                                                                                                                                                                                                                                                                                                   |      |         |         |         |         |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|---------|---------|---------|---------|
| <b>Anastrozole</b><br>- Take 1mg dose in the morning<br>- Take at the same time every day with food and water<br>- Do not take an extra dose if a dose is missed |      |      |      | <b>Onapristone - Dose _____ mg twice a day</b><br>- Take _____ (#) of _____ mg and _____ (#) of _____ mg<br>In the morning and in the evening<br>- Take at the same time every day with food and water<br>- Do not take an extra dose if a dose is missed<br>- Return unused study drug to the site at each visit |      |         |         |         |         |
| Day                                                                                                                                                              | Date | Dose | Time | Day                                                                                                                                                                                                                                                                                                               | Date | AM Dose | AM Time | PM Dose | PM Time |
| 1                                                                                                                                                                |      |      |      | 1                                                                                                                                                                                                                                                                                                                 |      |         |         |         |         |
| 2                                                                                                                                                                |      |      |      | 2                                                                                                                                                                                                                                                                                                                 |      |         |         |         |         |
| 3                                                                                                                                                                |      |      |      | 3                                                                                                                                                                                                                                                                                                                 |      |         |         |         |         |
| 4                                                                                                                                                                |      |      |      | 4                                                                                                                                                                                                                                                                                                                 |      |         |         |         |         |
| 5                                                                                                                                                                |      |      |      | 5                                                                                                                                                                                                                                                                                                                 |      |         |         |         |         |
| 6                                                                                                                                                                |      |      |      | 6                                                                                                                                                                                                                                                                                                                 |      |         |         |         |         |
| 7                                                                                                                                                                |      |      |      | 7                                                                                                                                                                                                                                                                                                                 |      |         |         |         |         |
| 8                                                                                                                                                                |      |      |      | 8                                                                                                                                                                                                                                                                                                                 |      |         |         |         |         |
| 9                                                                                                                                                                |      |      |      | 9                                                                                                                                                                                                                                                                                                                 |      |         |         |         |         |
| 10                                                                                                                                                               |      |      |      | 10                                                                                                                                                                                                                                                                                                                |      |         |         |         |         |
| 11                                                                                                                                                               |      |      |      | 11                                                                                                                                                                                                                                                                                                                |      |         |         |         |         |
| 12                                                                                                                                                               |      |      |      | 12                                                                                                                                                                                                                                                                                                                |      |         |         |         |         |
| 13                                                                                                                                                               |      |      |      | 13                                                                                                                                                                                                                                                                                                                |      |         |         |         |         |
| 14                                                                                                                                                               |      |      |      | 14                                                                                                                                                                                                                                                                                                                |      |         |         |         |         |
| 15                                                                                                                                                               |      |      |      | 15                                                                                                                                                                                                                                                                                                                |      |         |         |         |         |
| 16                                                                                                                                                               |      |      |      | 16                                                                                                                                                                                                                                                                                                                |      |         |         |         |         |
| 17                                                                                                                                                               |      |      |      | 17                                                                                                                                                                                                                                                                                                                |      |         |         |         |         |
| 18                                                                                                                                                               |      |      |      | 18                                                                                                                                                                                                                                                                                                                |      |         |         |         |         |
| 19                                                                                                                                                               |      |      |      | 19                                                                                                                                                                                                                                                                                                                |      |         |         |         |         |
| 20                                                                                                                                                               |      |      |      | 20                                                                                                                                                                                                                                                                                                                |      |         |         |         |         |
| 21                                                                                                                                                               |      |      |      | 21                                                                                                                                                                                                                                                                                                                |      |         |         |         |         |
| 22                                                                                                                                                               |      |      |      | 22                                                                                                                                                                                                                                                                                                                |      |         |         |         |         |
| 23                                                                                                                                                               |      |      |      | 23                                                                                                                                                                                                                                                                                                                |      |         |         |         |         |
| 24                                                                                                                                                               |      |      |      | 24                                                                                                                                                                                                                                                                                                                |      |         |         |         |         |
| 25                                                                                                                                                               |      |      |      | 25                                                                                                                                                                                                                                                                                                                |      |         |         |         |         |
| 26                                                                                                                                                               |      |      |      | 26                                                                                                                                                                                                                                                                                                                |      |         |         |         |         |
| 27                                                                                                                                                               |      |      |      | 27                                                                                                                                                                                                                                                                                                                |      |         |         |         |         |
| 28                                                                                                                                                               |      |      |      | 28                                                                                                                                                                                                                                                                                                                |      |         |         |         |         |

Patient signature and date