Memorial Sloan Kettering Cancer Center
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MSK PROTOCOL COVER SHEET

Basket Study of the Oral Progesterone Antagonist Onapristone ER (Apristor), Alone or In Combination With Anastrozole in Women with Progesterone Receptor Positive (PR+) Recurrent Granulosa Cell Tumor, Low Grade Serous Ovarian Cancer or Endometrioid Endometrial Cancer

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is an investigator initiated, open label, single institution basket study of the oral progesterone antagonist, onapristone ER (Apristor), alone or in combination with anastrozole, in women with selected progesterone receptor positive (PR+) recurrent gynecologic cancers. This study will enroll women with recurrent or advanced granulosa cell tumor, low grade serous ovarian cancer, or endometrioid endometrial cancer who have measurable disease and have progressed following at least one prior line of chemotherapy. Eligible patients will be progesterone receptor positive by immunohistochemistry (IHC), defined as ≥ 1% positivity displayed on archival tissue. Biopsy will be performed if no archival tissue is available or if archival tissue was taken more than 3 years prior .

Cohorts will be defined by histology with Cohort 1 enrolling patients with granulosa cell tumor to treatment with single agent onapristone ER 50 mg PO BID, Cohort 2 enrolling patients with low grade serous ovarian cancer to treatment with single agent onapristone ER, and Cohort 3 enrolling patients with endometrioid endometrial cancer to treatment with single agent onapristone ER. Cohorts 2 and 3 were closed to accrual in March of 2021 due to poor accrual as new treatments have become available for these diseases during the course of this study (endometrioid accrued 1 patient, low grade serous ovarian cancer accrued 5 patients). Cohort 1 completed accrual to stage 1 and has shown stable disease in 9 out of 14 patients patients with recurrent PR+ granulosa cell cancer treated with single agent onapristone ER at 50mg PO BID with ongoing responses lasting > 9 months in 2 patients. However, no RECIST 1.1 Criteria complete or partial responses have been seen. Cohort 4 will enroll patients with PR+ granuloasa cell tumor to onapristone ER 50mg PO BID in combination with anastrozole 1mg PO daily.

	Treatment	**Histology**	**Stage I**	**Stage II (expansion)**	**Response rate to be deemed worthy of further study**
Cohort 1	Onapristone ER	PR+ Granulosa cell tumor	Enroll 14 patients, if ≥ 1 response(s) expand to Stage II	Expand to a total of 23 patients	≥ 3/23
Cohort 2	Onapristone ER	PR+ Low grade serous ovarian cancer	Enroll 16 patients, if ≥ 2 responses expand to Stage II	Expand to a total of 25 patients	≥ 5/25
Cohort 3	Onapristone ER	PR+ Endometrioid endometrial cancer	Enroll 19 patients, if ≥4 responses expand to Stage II	Expand to a total of 36 patients	≥ 11/36
Cohort 4	Onapristone ER + Anastrozole	PR+ Granulosa cell tumor	Enroll 14 patients, if ≥ 1 response(s) expand to Stage II	Expand to a total of 23 patients	≥ 3/23

All enrolled patients will be treated at the recommended phase II dose (RP2D) of onapristone ER alone (cohort 1-3) or in combination with anastrozole (cohort 4) and continue on treatment until progression of disease, intolerable toxicity, or patient refusal. This study is expected to enroll between 34 and 43 patients, enrolling 1-2 patients per month. The study is expected to complete accrual within 12-24 months.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

The following objectives will apply to each of the three Cohorts (patient populations)

Primary Objective:

1) To evaluate the efficacy, in terms of response rate (CR or PR) of onapristone ER as a single agent or in combination with anastrozole, as determined by RECIST 1.1 response within 36 weeks of treatment, in patients with PR+ recurrent or advanced granulosa cell tumor, low grade serous ovarian cancer, or endometrioid endometrial cancer.

Secondary Objectives:

1) To evaluate the safety and tolerability of onapristone ER alone or in combination with anastrozole in this patient population.

2) To evaluate the duration of response, clinical benefit rate (CR, PR, SD lasting for ≥16 weeks) and progression free survival (PFS) of patients with PR+ recurrent or advanced low grade serous ovarian cancer, granulosa cell tumor or endometrioid endometrial cancer treated with onapristone ER alone or in combination with anastrozole.

Exploratory:

3) To correlate the level of PR positivity (as a continuous variable) with response to therapy (defined as complete or partial response) with onapristone ER alone or in combination with anastrozole.

4) To correlate the level of phosphorylated PR (as a continuous variable) with response to therapy with onapristone ER alone or in combination with anastrozole.

5) To correlate the level of PR target gene expression (as a continuous variable) with response to therapy (defined as complete or partial response) with onapristone ER alone or in combination with anastrozole.

3.0 BACKGROUND AND RATIONALE

3.1 Onapristone Background

Apristor, extended release onapristone, is a type I full progesterone antagonist that inhibits progesterone hormone-mediated PR activation and stabilizes PR association with corepressors. Onapristone has shown activity across multiple preclinical models of hormonally driven cancer. The development of immediate release onapristone was previously halted by Schering AG after liver function test abnormalities were observed; however, after further review the majority of these LFT elevations were found to be due to alternative causes and have not been seen as a significant issue with the reformulation of onapristone to an extended release version (Apristor). The clinical utility of Apristor is now being reevaluated and developed through Context Therapeutics.

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 [[1-4]].

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 unrelated AEs (anemia, thrombocytopenia and leucopenia) 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.

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 administrated 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_{∞} of approximately 13%.

3.2 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[5]. 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 promisimg 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 [6]. 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, 10 (56%) showed a PR and two (11%) durable SD (≥6 months), giving an overall tumor benefit rate of 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.

3.3 Anastrozole for Recurrent Granulosa Cell Cancer:

Anastrozole is a potent and selective nonsteroidal aromatase inhibitor. By inhibiting aromatase, the conversion of androstenedione to estrone, and testosterone to estradiol, is prevented, thereby decreasing tumor mass or delaying progression in patients with tumors responsive to hormones. Anastrozole causes an 85% decrease in estrone sulfate levels.

Aromatase inhibitors are commonly used to treated recurrent granulosa cell tumors based on low response rates to chemotherapy and historically high rates of ER/PR expression within these tumors.However, objective response rate remains low, and was found to be 2.5% in the prospective phase II PARAGON study on anastrozole 1mg po QD in patients with recurrent granulosa cell tumors (Banerjee, JCO, 2018).

3.4 Rationale for Current Study:

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 [3]. These are hormonally driven gynecologic cancers which generally have poor responses to chemotherapy and limited treatment options. This phase II study currently ongoing at Memorial Sloan Kettering Cancer Center has enrolled 14 patients with recurrent PR+ granulosa cell cancer and exhibited SD in 9 out of 14 patients treated, with minimal adverse events reported. We now seek to test the combination of Onapristone ER in combination with anastrozole to hopefully enhance the response rate in patients with PR+ granulosa cell cancer.

While prospective data is lacking in patients with low grade serous ovarian cancer the retrospective response rate to chemotherapy is 4%, and 9% to available hormonal therapies [7, 8]. Granulosa cell, 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[9]. Endometrial cancer also has limited options with a 13% response rate to chemotherapy in the second line [10]. Megestrol acetate is the only systemic treatment FDA approved specifically for endometrial cancer 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 [11].

Apristor (onapristone ER) is a well-tolerated oral full progesterone antagonist which has shown promising preliminary findings in gynecologic cancer based on a dose escalation study [[3]]. Granulosa cell ovarian cancer, low grade serous ovarian cancer and endometrioid endometrial cancer are hormonally driven gynecologic cancers with poor response rates to chemotherapy and limited treatment options available. We hypothesize that oral onapristone ER 50 mg PO BID will be active across multiple histologic types of PR+ gynecologic cancer. To test this hypothesize we will implement a basket study of onapristone ER in PR+ granulosa cell ovarian cancer, low grade serous ovarian cancer and endometrioid endometrial cancer with recurrent or advanced measurable disease, which has progressed following at least one line of chemotherapy and in combination with anastrozole 1mg po QD will be active in patients with PR+ granulosa cell tumors..

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is an open-label, single institution, investigator-initiated study of extended release onapristone alone or in combination with anastrozole in patients with PR+ granulosa cell, low grade serous ovarian cancer, or endometrioid endometrial cancer who have measurable disease and have progressed following at least 1 prior line of chemotherapy. These histologies have been chosen for further exploration based on the results of an earlier phase I study of extended release onapristone showing preliminary efficacy in these histologies, the hormonally responsive nature of these histologies, and the limited available options for systemic therapy of granulosa cell tumors, low grade serous ovarian cancer, and endometrioid endometrial cancer, with historically low response rates to systemic therapy.

This study will determine the efficacy of extended release onapristone and determine those gynecologic histologies worthy of further development.

4.2 Intervention

Patients with the histologies of interest (granulosa cell tumor, low grade serous ovarian cancer, or endometrioid endometrial cancer) with recurrent disease will be screened for eligibility. Patients must have archival tissue available which is positive for expression of the progesterone receptor (≥ 1% PR+ by IHC). If archival tissue has not previously been screened for presence of the progesterone receptor as part of routine diagnostic review, then archival tissue must be available for IHC analysis. Patients who do not have archival tissue available, or have archival tissue that was taken more than 3 years prior, will undergo a biopsy in line with what is medically appropriate for their disease. Patients will not be put at undue risk to obtain fresh tissue biopsy to determine study eligibility as procedures more invasive than a core biopsy should not be utilized; in other words, a procedure to obtain

biopsy should have a serious/severe complication risk no greater than 2%. The ICH analysis on baseline samples will be non-billable.

All enrolled patients will be treated with onapristone ER at the recommended phase 2 dose of 50mg PO BID or in combination with anastrozole 1mg po QD (cohort 4). Study drugs will be self-administered by patients. Patients will take onapristone ER and anastrozole with food and water. A cycle is 28 days. Patients will be required to maintain a pill diary to record each dose of drug taken. All toxicities will be graded using CTCAE version 5.0. Toxicities will be evaluated during physician assessments performed every 2 weeks during the first cycle and every 4 weeks during subsequent cycles of treatment with onapristone ER with or without anastrozole.

Patients will continue to receive study treatment until disease progression (as defined by RECIST 1.1), unacceptable toxicity or withdrawal of consent.

All cohorts (granulosa cell tumor, low grade serous ovarian cancer, endometrioid endometrial cancer) will enroll in parallel, with expansion from stage I to stage II when the prespecified response criteria are met for each cohort as described in the table below.

	Treatment	**Histology**	**Stage I**	**Stage II (expansion)**	**Response rate to be deemed worthy of further study**
Cohort 1	Onapristone ER	PR+ Granulosa cell tumor	Enroll 14 patients, if ≥ 1 response(s) expand to Stage II	Expand to a total of 23 patients	≥ 3/23
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Cohort 3	Onapristone ER	PR+ Endometrioid endometrial cancer	Enroll 19 patients, if ≥4 responses expand to Stage II	Expand to a total of 36 patients	≥ 11/36
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5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Pharmacokinetics

In a Phase 1 dose escalation trial, Apristor AUC and Cmax were dose-proportional across dose levels. Average Tmax was 3.01 hours (2.71-3.2) vs 1.84 hours for 10-50 mg with a 60% (+/- 20) relative bioavailability. Steady state was attained before day 8 and the mean minimum concentrations at steady state were up to 5 times those obtained at day 1. There was no evidence of accumulation at day 57. The observed mean t1/2 was approximately 18.01 hours (range, 13.9 to 37), consistent with steady state achievement before day 8. Plasma concentration versus time curves suggest biphasic elimination [[3]].

5.2 Onapristone Extended Release Tablets

Onapristone is a yellow to green solid with a melting point of 155°C. Onapristone is a weak base with a pKa of 5.15 (± 0.15). The logP is 4.03 and the logD is 3.97. Onapristone is slightly to very slightly soluble in aqueous buffer solutions at acidic pH up to pH 5.0 (pH 1.2, 2.0, 3.0 and 5.0). There is a decrease in solubility at pH values 6.0 – 8.0. Multiple drug product formulations of onapristone have been developed for evaluation throughout the clinical development program. The focus of further development and in this study will be Onapristone ER Tablets.

Onapristone extended release tablets are available in 10mg and 20mg form. Patients will take 50 PO BID in the form of two 20 mg tablets and one 10 mg tablet taken with food and water twice daily. Uncoated round tablets are being phased out as inventory diminishes. Patients enrolled to this study will be treated with either coated or uncoated tablets, depending on available inventory. The coated tablets used in this study will be pink and yellow film coated oval tablets (10 and 20mg, resp.). Coated and uncoated tablet core formulations are the same to release the drug at similar rates. The coating is water soluble.

Quantitative Composition of Onapristone Extended-Release Tablets

Component	Quality Standard	Function	Amount (mg)			
			2.5 mg	5 mg	10 mg	20 mg
Onapristone[1]	In-house	API	2.50	5.00	10.00	20.00
Microcrystalline cellulose	USP and Ph.Eur.	filler	20.5	20.5	20.5	20.5
Lactose monohydrate	USP and Ph.Eur.	filler	10.25	20.50	41.00	82.00
Pregelatinized Starch	USP and Ph.Eur.	disintegrant	10.00	20.00	40.00	80.00
Hydroxypropyl Methylcellulose	USP/NF and Ph.Eur.	Binder/ modified release agent	16.50	33.00	66.00	132.00
Colloidal silicone dioxide	USP/NF and Ph.Eur.	glidant	0.25	0.50	1.00	2.00
Magnesium stearate	USP/NF and Ph.Eur.	lubricant	0.25	0.50	1.00	2.00

Total tablet weight (mg)	-	-	50	100	200	400

[1]The weight of drug substance is adjusted per the assay value of onapristone on an "as-is" basis. As required, the difference in weight is adjusted with hydroxypropyl methylcellulose.

5.3 Onapristone Storage and Labeling

The tablets are stored under ambient conditions, at 15-30 °C.

Select batches of onapristone ER tablets are on ICH stability programs at 25 ± 2 °C/60 ± 5% (long-term condition) and 40 ± 2 °C/75 ± 5% (accelerated condition). An intermediate condition of 30 ± 2 °C/65 ± 5% RH is being utilized as backup condition. For batches with the longest-term stability data, no significant changes in the appearance, potency (assay), impurity profile or dissolution profile have been observed after 6 months at the accelerated storage condition (40 °C/75% RH) and 18 months at the long-term storage condition (25 °C/60% RH). Based on ICH Q1A(R2) and Q1E guidance, the shelf life for ER tablets is currently set at 30 months.

5.4 Anastrozole

Anastrozole is an aromatase inhibitor which is commercially available and a standard of care treatment for recurrent granulosa cell cancer. It should be stored at room temperature. Commercial supply will be used. Patients will be prescribed anastrozole 1mg PO QD. Anastrozole will be taken once daily in the AM with patients morning dose of onapristone ER.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Histologically confirmed diagnosis at MSK of either (1) granulosa cell ovarian cancer, (2) low grade serous ovarian/ primary peritoneal cancer, or (3) endometrioid endometrial cancer; with PR expression ≥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 MSK.
- Measurable disease as defined by RECIST 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 ≥10mm when measured by CT or MRI. Lymph nodes must be ≥15mm in short axis when measured by CT or MRI
- Patients must have had one prior chemotherapy regimen for management of disease. Note: additional lines of chemotherapy, biologic or immunotherapy are allowed.
- Recovery from effects of recent surgery, radiotherapy, or chemotherapy
  - At least 4 weeks out from their last dose of radiation therapy
  - At least 4 weeks post-op from any major surgical procedure
  - At least 3 weeks out from their last dose of chemotherapy and/or biologic/targeted therapy
- Must be ≥ 18 years of age
- Karnofsky Performance Status (KPS) of ≥ 70%

- Women of child-bearing potential must have a negative pregnancy test within 14 days prior to commencement of study treatment
- Women of child bearing potential must use an effective form of contraception during study and for at least 6 months after completion of study treatment
- Laboratory Test Findings performed within 14 days prior to initiation of study drug showing:
    - Bone marrow function:
        - Absolute neutrophil count (ANC) ≥ 1,000/mcL
        - Platelets ≥ 75,000/mcL
        - Hemoglobin ≥ 8 g/dL
    - Renal function:
        - Creatinine ≤ 1.5 x ULN
    - Hepatic function:
        - Bilirubin ≤ 1.5 x ULN
        - AST and ALT ≤ 2.5 x ULN
- Resolution of all acute toxic effects of prior therapy to NCI CTCAE (Version 5.0) Grade ≤ 1, with the exception of unresolved Grade 2 neuropathy and Grade 2 alopecia, which are allowed
- Patient has recovered from any prior radiotherapy
- Patients must be able to swallow tablets whole, without crushing

6.2 Subject Exclusion Criteria

- History of another invasive malignancy (other than non-melanoma skin cancer or curatively treated in situ carcinoma) with evidence of disease within the past 3 years
- History of prior hormonal therapy (i.e., megesterol acetate, tamoxifen or aromatase inhibitors) for treatment of cancer within 28 days before starting study drug
- Any psychological, familial, sociological or geographic condition that would potentially hamper compliance with the study protocol
- Known brain metastasis which have not been treated or showed stability for ≥ 6 months
- Patient has received an oral or IV corticosteroid within the prior 28 days and requires chronic corticosteroid therapy (excludes use of steroid premeds for CT allergy)
- Uncontrolled hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 95mmHg) despite medical treatment. Patients with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive treatment.
- Clinically significant heart disease as evidenced by myocardial infarction or arterial thrombotic event within the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class II-IV heart disease or cardiac ejection fraction measurement of < 50% at baseline
- Refractory nausea and vomiting, requirement for parenteral hydration and/or nutrition, drainage gastrostomy tube, malabsorption, external biliary shunt, or significant small bowel resection that would preclude adequate study drug absorption

- Anticipated or ongoing administration of anti-cancer therapies other than those administered in this study
- 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.

7.0 RECRUITMENT PLAN

Patients will be recruited from the patients seen by the Gynecologic Medical Oncology (GMO) Service, Department of Medicine, at Memorial Sloan Kettering Cancer Center (MSKCC). The investigator will screen patients with granulosa cell ovarian cancer, low grade serous ovarian cancer, and endometrioid endometrial cancer to see if they are eligible for this trial.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment.

8.0 PRETREATMENT EVALUATION

Screening:

- Signature of screening informed consent if PR testing has not yet been performed (signature of prescreening consent is not needed if PR status is already available from archival tissue)
- Tumor biopsy or paracentesis, if no archival tissue is available within past 3 years
- Verification of ≥1% PR+ by IHC in tumor tissue, if not previously performed

To be completed within 30 days prior to start of study drug:

- Signature of treatment informed consent following inclusion and exclusion review and determination of patient eligibility for the study
- Physical exam and vital signs (height, weight, pulse, temperature, blood pressure)
- Karnofsky Performance Status (KPS)
- 12-lead electrocardiogram (ECG)
- Baseline radiographic tumor assessment (CT or MRI of abdomen and pelvis; CT of chest) with documentation of sites of disease per RECIST (version 1.1)
- Bone density (if not performed within 12 months prior to start of therapy)

To be completed within 14 days prior to start of study drug:

- Pregnancy test in women of child bearing potential
- Blood sampling for:
  - CBC with differential
  - Comprehensive Metabolic Panel (Na, K, Cl, CO2, BUN, CREAT, Ca, Glucose, Bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT)
  - Coagulation tests (PT, PTT, INR)

9.0 TREATMENT/INTERVENTION PLAN

9.1 Treatment Plan

Enrolled patients will initiate treatment with onapristone ER 50 mg by mouth twice daily, about 12 hours apart, and anastrozole 1mg po QD in AM (if in cohort 4) beginning Day 1 of Cycle 1. A Cycle is 28 days. Onapristine ER tablets should be swallowed whole with a glass of water and food l. Onapristone ER and anastrozole should be taken at the same times each day. Missed doses will not be made-up. Vomited doses should not be retaken. All doses and missed doses will be recorded in the patient's pill diary. Patients will remain on treatment with onapristone ER 50 mg PO BID alone (cohorts 1-3) or with anastrozole 1 mg po QD (cohort 4) (with dosage adjustments as described below) until POD, unacceptable toxicity or withdrawal of consent.

While on study, patients will return for assessments with a treating physician every 2 weeks during the first cycle, and then every 4 weeks. Vital signs, toxicity assessment and blood work will be performed at each start of cycle visit. The pill diary will be collected, and a new drug supply and pill diary will be provided. A +/- 4 day window is allowed for each start of cycle assessment.

Within 30 days of starting treatment, every 8 weeks from Cycle 1 Day 1 while on treatment, and at end of study, patients will have a CT of chest, abdomen and pelvis performed, or MRI of abdomen and pelvis with CT of chest. Best overall response should be confirmed with repeat imaging performed at ≥ 4 weeks. There is a +/- 7 day window for completion of interval tumor assessments by imaging.

An optional research non-billable tumor biopsy will be performed at end of treatment in consenting patients with accessible disease.

9.2 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 ≥ 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 ≤ 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 ≤ Grade 1 or baseline, and then onapristone ER resumed with dose reduction as per table below.

- If onapristone ER is held for ≤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 drug should be permanently discontinued. Patients may continue on anastrozole as a single agent if onapristone ER is held Onapristone dose reductions will occur as per the table below:

Starting Dose	50 mg PO BID
Dose Reduction #1	30 mg PO BID
Dose Reduction #2	10 mg PO BID
Dose Reduction #3	Permanently Discontinue

9.3 Dose Adjustment for Anastrozole Toxicity

No dose adjustments of anastrozole will occur.

- If Grade 1 or 2 toxicities occur, give supportive care per institutional guidelines.

- If ≥ Grade 3 toxicities occur that are considered potentially related to anastrozole (with the exception of osteoporosis or alopecia) hold anastrozole until the toxicity resolves to ≤ Grade 1 (unless was Grade 2 at baseline, then when returns to baseline).

- If anastrozole is held for ≤28 days, it may be restarted at the same dose at the discretion of the treating physician

- If anastrozole is held for >28 days, the drug should be permanently discontinued

Patients may continue on onapristone ER as a single agent if anastrozole is held

10.0 EVALUATION DURING TREATMENT/INTERVENTION

	Screening	Pre-Treatment[9]	Day 1[3]; Cycle 1	Day 15; Cycle 1[3]	Day 1; Cycle 3, 5, 7… (odd cycles)[3]	Day 1; Cycle 2, 4, 6… (even cycles)[3]	End of Study Treatment Follow up[5]	Safety 30 day & Survival Follow up
Informed Consent	X	X						
History & Physical		X	X	X[7]	X[7]	X[7]	X	
Toxicity Assessment		X	X	X	X	X	X	X[11]
Vital Signs		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	
KPS		X	X	X	X	X	X	
ECG		X[2]						
Radiographic Tumor Assessment of Chest/ Abd/ Pelvis		X[4]			X[4]		X[4]	
CBC with Differential		X	X[10]	X	X	X	X	
Pregnancy Test (for patients of child bearing potential)		X				X		
Comprehensive Metabolic Panel		X	X[10]	X	X	X	X	
Coagulation Tests		X						
Bone Density	X							Every 12 months (±14 days)
Tumor Biopsy	X[6], and IHC testing						X[6]	
Dispense Onapristone ER (and anastrozole, if cohort 4)			X[8]		X[8]	X[8]		
Chart review for PD								Every 3 months (±14 days) [12]
Survival status								Every 3 months (±14 days) [12]

1: Vital signs: blood pressure, heart rate, temperature and weight. Height need only be taken on Cycle 1, Day 1.

2: Hypokalemia should be corrected prior to ECG collection

3: All visits have a +/- 4 day window unless otherwise noted

4: Radiographic tumor assessment of abdomen and pelvis may be performed using CT or MRI.Chest imaging chould occur by CT. There is a +/- 7 day window for completion of interval tumor assessments by imaging. Imaging should be performed every 8 weeks following Day 1 of treatment. Radiographic tumor assessment at end of study treatment should only be completed for patients coming off study for reasons other than progression and only if it has been greater than 4 weeks since the last tumor assessment.

5: End of Study Treatment Visit should happen within 30 days of last dose of study drug.

6: Patients without adequate archival tissue from within the past 3 years available will have a biopsy performed, as medically appropriate for their disease. Patients who had progressive disease and consent for an end of treatment biopsy will have an optional non-billable tumor biopsy performed at end of treatment.

7: Includes recording of concurrent medications and focused physical exam. There is a +/- 4 day window allowable for each start of Cycle assessment.

8: Pill diary and remaining pills should be collected and new pill diary and 1 month supply of study drug should be given to patient. Anastrozole will be prescribed by the treating physician and dispenced as commercial supply.

9: Screening assessments should be completed within 30 days prior to treatment with the exception of CBC with differential, comprehensive metabolic panel, coagulation tests, and pregnancy test which should be completed within 14 days prior to treatment.

10: Cycle 1 Day 1 blood tests can be omitted if Screening blood tests are completed within 72 hours from Cycle 1 Day 1.

11: A safety follow-up visit or phone call will be conducted 30 days (± 7 days) after the last dose of onapristone ER. AE should be monitored.

12: Survival follow-up phone call will be conducted every 3 months from 30 day safety follow-up visit until the patient initiates a new treatment.

For the patients who came off treatment due to unacceptable toxicity or withdrawal of consent, reviewing medical records for progression status will stop once the patient becomes POD.

10.1 Tumor Biopsy

Tumor biopsies will potentially be performed at two time points during this study; a biopsy will be performed at screening if no archival tissue is available and an optional biopsy may be performed at end of treatment.

If the patient has archival tissue available that is appropriate for PR IHC staining (block or unstained slides) or that has already had PR IHC completed, and is no more than 3 years old, then archival tissue may be used. If ≥ 1% PR tumor staining is seen on ≥ 1 slide the tumor will be considered to be PR+.

An optional tumor biopsy will be performed at end of treatment in those patients who have POD, consent to biopsy, and have accessible disease.

Biopsy samples should be fixed in 10% formalin and paraffin embedded. **In cases where a reasonable size biopsy is obtained (i.e., excisional biopsy, 18 gauge needle), such that the pathologist feels there is adequate sample for preparation of both a frozen and fixed specimen, a fresh frozen biopsy should also be collected**. At a minimum, enough tissue should be collected (by FNA or Core) for generation of a FFPE block for H&E and IHC analysis. At a maximum 2 cores should be collected.

Lesions with the greatest change in dimensional size based on interval evaluation are the recommended lesions to be excised. Whenever possible, biopsies at POD should be performed within 3 days of study drug discontinuation. Biopsies obtained at the time of progressive disease will be used to investigate potential mechanisms of acquired resistance. Biopsy samples will be analyzed for level of PR positivity by IHC to determine if the progesterone receptor is downregulated during treatment with onapristone ER.

10.2 Correlative Studies

The degree of PR expression levels will be determined using standard immunohistochemistry methodology on all tissue and reported as percent tumor cells with PR staining. In cases where no PR results are available, one-three 5 micrometer superplus frost slides will be used for IHC testing. This testing will be performed at the Memorial Sloan Kettering Cancer Center CLIA approved clinical pathology laboratory using the Dako progesterone receptor antibody. Upon receipt of the slide in the clinical laboratory, results will be reported within 72 hours. The relationship between tumor response and degree of PR expression, and/or PR signaling, will be examined.

Additional exploratory biomarkers will be evaluated on FFPE tissue , including phosphorylated PR and PR target gene expression. If ≥ 1% phosphorylated Ser294 PR (pPR) tumor staining is seen on ≥ 1 slide the tumor will be considered to be pPR+. Nuclear localization of pPR will also be evaluated. PR target gene analysis will be completed using the NanoString nCounter oncology panel system. NanoString analysis will require 25 ng of FFPE tissue.

11.0 TOXICITIES/SIDE EFFECTS

11.1 Toxicities to Date with 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 [[1-4]].

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 unrelated AEs (anemia, thrombocytopenia and leucopenia) 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.

Common (>10%): nausea, asthenia, gamma glutamyltransferase increased

Occasional (4-10%): abdominal distention, abdominal pain, diarrhea, dry mouth, fatigue, peripherial edema, pain, ALT and AST elevated, bilirubin increased, alkaline phosphate increased, LDH increased, LFT test abnormal, decreased appetite, hyperkalemia, tendonitis, agistation, hot flush, hypertension

11.2 Potential for Drug-Drug Interaction:

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 Table below).

Patients will be instructed to avoid concomitant use of aspirin, NSAIDs, and prostaglandins. Intake of paracetamol up to 4 g/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

CyP3A Inhibitors	**CyP3A Inducers**	**CyP3A Substrates**
Strong	**Strong**	**Sensitive**
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

CyP3A Inhibitors	CyP3A Inducers	CyP3A Substrates
saquinavir		indinavir
telaprevir		fluticasone
telithromycin		lopinavir
voriconazole		lovastatin
		lurasidone
Moderate	**Moderate**	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		vardenafil
verapamil		
Weak	**Weak**	**Narrow therapeutic window**
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

CyP3A Inhibitors	CyP3A Inducers	CyP3A Substrates
		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

11.3 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 section 10. A safety follow-up visit will be conducted 30 days (+/- 7 days) after the last dose of onapristone ER.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.1 Definitions

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

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their

disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

12.2 Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

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

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and

reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and $\geq$10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans), but NOT lung.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. PET-CT scans are not always done with oral and IV contrast. In addition, the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed. For these reasons, we will not allow PET-CT use for RECIST 1.1 response criteria.

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

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

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

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

12.4 Response Criteria

12.4.1 ***Evaluation of Target Lesions***

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

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

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

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.4.2 *Evaluation of Non-Target Lesions*

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

Non-CR/Non-PD: Persistence of one or more non-target lesion(s).

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.4.3 *Evaluation of Best Overall Response*

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**

PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

13.0 CRITERIA FOR REMOVAL FROM STUDY

Study treatment will be discontinued for the following reasons:

- Progression of disease (unless patient agrees to continue treatment past progression)
- Persistent or unacceptable toxicity despite appropriate dose reductions
- Withdrawal of consent
- If in the opinion of the investigator continuation on study poses unreasonable risks to the patient. This might include patients who fail to return for adequate follow-up, hampering the ability to monitor toxicities

Any patient discontinuing study drug should be seen at 30 days post discontinuation for the evaluations outlined in the study schedule. The patient's tumor status should be assessed clinically and, if appropriate, disease progression should be confirmed by radiological assessment.

After discontinuation of the study medication at any point in the study, all ongoing AEs or SAEs must be followed until resolution unless, in the investigator's opinion the condition is unlikely to resolve due to the patients underlying disease, or the patient is lost to follow up. All new AEs and SAEs occurring during the 30 calendar days after the last dose of study medication must be recorded, reported if applicable and followed to resolution as above. Patients should be contacted at least 30 days after discontinuing study medication to collect and /or complete AE information. Any untoward event occurring subsequent to the 30-day follow-up AE reporting period that the investigator assesses as possibly related to the study medication should also be reported as an AE.

Any patient, who has not yet shown objective disease progression, should continue to be followed as per RECIST 1.1.

The study and/or individual Cohorts may be discontinued if it is found that it is not feasible to reach the planned outcomes.

13.1 Treatment Past Progression:

If a patient is found to have progression of disease by RECIST 1.1 criteria, but in the opinion of the treating clinician is felt to potentially still derive benefit, after discussion with study PI, the patient may consent to continue with protocol directed treatment. If the patient decides to continue receiving treatment, the patient will be asked to sign a separate consent form. The treating clinicans discussion of treatment past progression with the patient should be documented in the medical record.

14.0 BIOSTATISTICS

This is a single institution, investigator initiated, open label, basket study exploring the efficacy of onapristone ER in PR+ recurrent or advanced gynecologic cancer that has been designed as three parallel Simon 2-Stage studies testing the recommended phase 2 dose of onapristone ER as a single agent or in combination with anastrozole in histologies of interest.

Three histologies of interest are being examined:

Cohort 1: Granulosa cell ovarian cancer (onapristone single agent)

Cohort 2: Low grade serous ovarian cancer (onapristone single agent)

Cohort 3: Endometrioid endometrial cancer (onapristone single agent)

Cohort 4: Granulosa cell ovarian cancer (onapristone in combination with anastrozole)

The null hypothesis for each basket is based on poor historical rates to systemic therapies in these histologies. While prospective data is lacking in patients with low grade serous ovarian cancer the retrospective response rate to chemotherapy is 4%, and 9% to available hormonal therapies [7, 8, 12, 13]. Granulosa cell, the most common type of sex-cord stromal ovarian cancer, generally has poor response rates to chemotherapy and is commonly treated with hormonal strategies, most commonly aromatase inhibitors, though the response rate to anastrozole in recurrent granulosa cell tumors is 2.5%. [9]. Endometrial cancer also has limited options with a 13% response rate to chemotherapy in the second line [10]. Megestrol acetate is the only systemic treatment FDA approved specifically for endometrial cancer 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 [11]. Tamoxifen as a single agent has a response rate of 10% in recurrent endometrial cancer[14, 15] .

A short-coming of this design is that a basket study which implements multiple independent two-stage designs has a higher overall false-positive rate than a typical phase II study[16]. However, to modulate this effect we have limited this study to 4 baskets/cohorts. Sample size calculations are based on the Simon two-stage minimax design.

For Cohort 1 if ≥ 1/14 complete or partial responses are seen by RECIST 1.1 criteria within 6 months of treatment (stage I) then the study will expand to stage II. If a total of ≥ 3/23 responses (inclusive of the original 14 patients from stage I) are seen then this Cohort will be deemed worthy of further investigation. This assumes an unacceptable response rate of 3% and a desirable response rate of 20% with a Type I error rate of 5% and a Type II error rate of 15%.

For Cohort 2 if ≥ 2/16 complete or partial responses are seen by RECIST 1.1 criteria within 6 months of treatment (stage I) then the study will expand to stage II. If a total of ≥ 5/25 responses (inclusive of the original 16 patients from stage I) are seen then this Cohort will be deemed worthy of further investigation. This assumes an unacceptable response rate of 10% and a desirable response rate of 30% with a Type I error rate of 10% and a Type II error rate of 10%.

For Cohort 3 if ≥ 4/19 complete or partial responses are seen by RECIST 1.1 criteria within 6 months of treatment (stage I) then the study will expand to stage II. If a total of ≥ 11/36 responses (inclusive of the original 19 patients from stage I) are seen then this Cohort will be deemed worthy of further investigation. This assumes an unacceptable response rate of 20% and a desirable response rate of 40% with a Type I error rate of 10% and a Type II error rate of 10%.

For Cohort 4 if ≥ 1/14 complete or partial responses are seen by RECIST 1.1 criteria within 6 months of treatment (stage I), then the study will expand to stage II. If a total of ≥ 3/23 responses (inclusive of the original 14 patients from stage I) are seen then this Cohort will be deemed worthy of further investigation. This assumes an unacceptable response rate of 3% and a desirable response rate of 20% with a Type I error rate of 5% and a Type II error rate of 15%.

Secondary/Exploratory objectives:

To evaluate the safety and tolerability of onapristone ER alone or in combination with anastrozole in these patient populations toxicity data will be collected at each visit and tabulated with grading by CTCAE Version 5 criteria. Dose holding and modifications will occur as described in section 9.2

The objective response rate and progression free survival (PFS) will be analyzed separately for each disease type (basket/cohort 1,2,3 and4). PFS will be defined from the start of treatment to disease progression or death (whichever occurs first) or last follow-up. Kaplan Meier estimates will be used to estimate the median PFS and 2-year rate. Response will be determined by RECIST 1.1 criteria. Objective response is defined as complete or partial response by week 36 or best overall response. Duration of response will be reported for the subset of patients who experience an objective response.Clinical Benefit Rate (CBR) is defined as the percentage of patients who have achieved a complete response, partial response, or stable disease lasting ≥ 16 weeks.

Patients coming off study prior to first post-baseline assessment for reasons other than toxicity or progression may be replaced following discussion with study PI, if deemed appropriate. Patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response Accrual in each cohort will continue until the required number of evaluable patients in each cohort are accrued. Responses will be confirmed by repeat imaging performed at least 4 weeks after confirmed response. Binomial proportions will be assumed when calculating the 2 sided 80% confidence interval around the objective response rate for each cohort separately.

To correlate the level of PR positivity (measured by immunohistochemsirty as a continuous variable), the level of phosphorylated PR (as a continuous variable) and the level of PR target gene expression (as a continuous variable) with response to therapy (defined as complete or partial response by week 36) with onapristone ER, a non-parametric test, such as the Wilcoxon test, will be used to test whether the PR levels (continuous variable) are different in the 2 groups of responders (complete or partial response) vs non responders. Each cohort/basket will be analyzed separately.

Sample Size:

Cohort 1 has enrolled 14 patients and stopped at Stage 1. Cohorts 2 (5 patinets enrolled) and 3 (1 patient enrolled) closed early due to poor accrual. Cohort 4 will enroll 14-23 patients.This study is expected to enroll between 34 and 43patients. Accrual of 1-2 patients per month is anticipated. The study is expected to complete accrual within 12- 24 months.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

This is a non-randomized study

16.0 DATA MANAGEMENT ISSUES

A Clinical Research Coordinator (CRC) will be assigned to the study. The responsibilities of the CRC include data collection, abstraction and entry, data reporting, and problem resolution and prioritization.

The data collected for this study will be entered into Medidata, a secure database. Source documentation will be available to support the computerized patient record.

The estimated rate of accrual will be 1-2 patients per month. All patients will remain on treatment until POD, intolerable toxicity, self-discontinuation of study treatment, or removal from study for any other reason.

16.1 Quality Assurance

Registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled —Policy of the

National Cancer Institute for Data and Safety Monitoring of Clinical Trials‖ which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM

Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Clinical Research Portal.

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center‘s Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored,

in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

17.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted

within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

- The report should contain the following information:
- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

For IND/IDE protocols: The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

17.2.1

All SAEs need to be reported to the Context Therapeutics within 5 days of notification of the event. The MSK SAE form should be sent to:

Tarek Sahmoud, MD, PhD
Chief Medical Officer
Context Therapeutics
P: (267) 454-8755
E: tsahmoud@contexttherapeutics.com

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

Appendix A: Pill Diary

Appendix B: KPS Scale

Appendix C: Radiation Dosimetry