A Phase II Trial of OnapriStone in CoMbInation with FuLvestrant for Patients with ER-positive, and HER2-negative Metastatic Breast Cancer after Progression on Endocrine therapy and CDK 4/6 Inhibitors

Short Title:

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PROTOCOL SIGNATURE PAGE

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The signature below confirms that I have read this protocol 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.

_____ _____

Investigator Signature Date

_____

Printed Investigator Name

_____

Site Name

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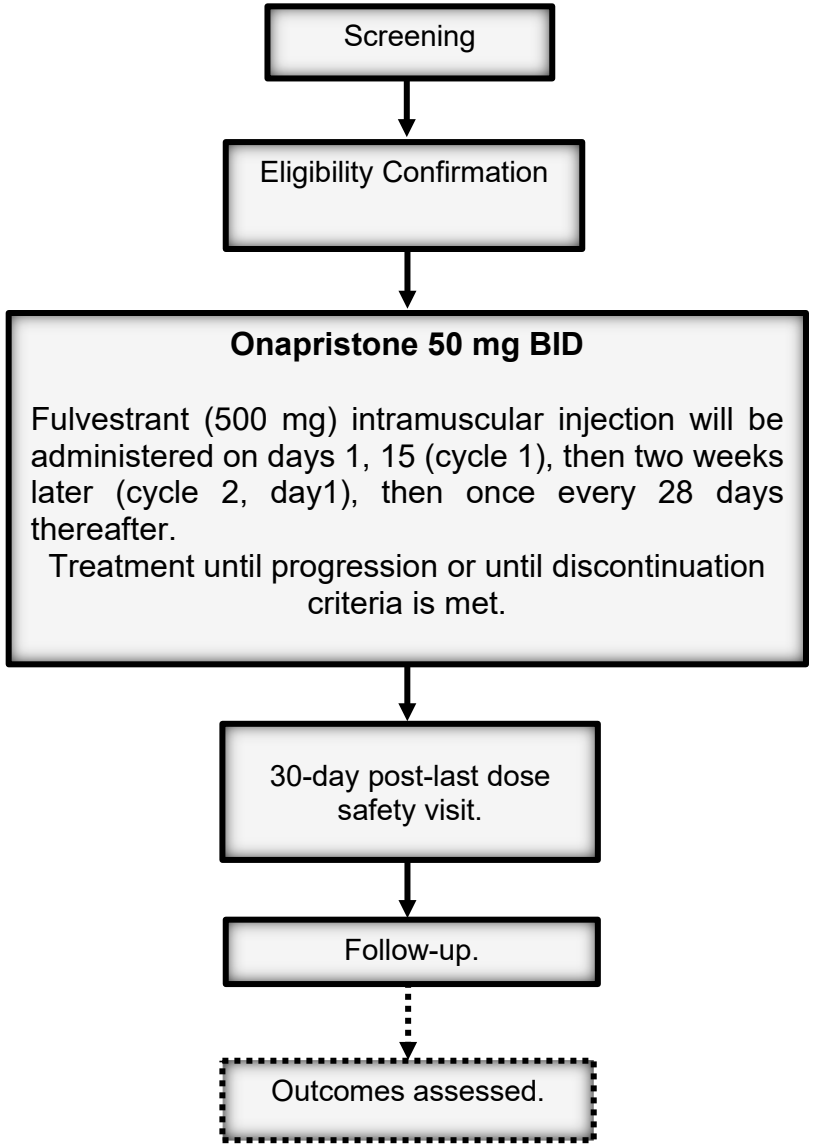
PROTOCOL SUMMARY

Title	A Phase II Trial of OnapriStone In CoMbInation with FuLvestrant for Patients with ER-Positive, and HER2-Negative Metastatic Breast Cancer after Progression on Endocrine therapy and CDK 4/6 Inhibitors
IND Sponsor	Sponsor-investigator
Study Chair	Sailaja Kamaraju, MD, MS
Principal Investigator	Kari Wisinski, MD
Study Sites	UW Carbone Cancer Center, Medical College of Wisconsin, and select Wisconsin Oncology Network sites.
Clinical Trial Phase	Phase II
Study Disease	ER-positive, (PgR-positive or PgR negative) and HER2-negative metastatic breast cancer.
Main Eligibility Criteria	Patient has advanced (locally advanced or locoregionally recurrent not amenable to curative therapy or metastatic ER+/PgR+/-, and HER2 negative) breast cancer with disease progression on CDK4/6 inhibitor-based therapy.
Primary Objective	Estimate the objective response rate (ORR).
Primary Endpoint	Best overall response of CR or PR, as per RECIST 1.1.
Secondary Objectives	1. To evaluate progression-free survival rate (PFS). 2. Estimate the disease control rate (DCR). 3. To describe time to response and duration of response. 4. To evaluate safety and tolerability.
Secondary Endpoints	1. Time from date of enrollment to the date of first documented disease progression or death due to any cause. 2. Best overall response of CR, PR or SD lasting for ≥ 24 weeks, as per RECIST 1.1. 3. Time to response: Time from registration to first documented response (CR or PR). Duration of response: Time between the first date of documented response to progression or death due to breast cancer. 4. Type, frequency and severity of adverse events and laboratory abnormalities according to CTCAE version 5.0. 5. Biomarker correlatives.
Study Design	This is a phase II single-arm trial.

Study Intervention Description	All patients will receive onapristone 50 mg p.o. BID daily and fulvestrant (500 mg) intramuscular injection on days 1, 15 (cycle 1), then two weeks later (cycle 2, day1), then once every 28 days thereafter. A cycle is defined as 28 days. There will be no breaks between dosing cycles.
Number of Subjects	A total of 39 subjects will be enrolled in the study.
Estimated Time to Complete Enrollment:	Approximately two years.

STUDY SCHEMA



STUDY CALENDAR

Study Procedures	**Screening**[1]	**Cycle 1 (1 cycle = 28 days)** (± 2 days)			**Cycle 2 and beyond (1 cycle = 28 days)** (± 3 days)	**Progression/ End of Treatment Visit**	**Safety Visit**[2,3] (±14 days)	**Follow-up (12 months) Every 3 months** (±14 days)
Study Day/Visit Day	**Day – 30 to Enrollment**	**1**[5]	**8**	**15**	**1**			
Informed Consent	X							
Demographics	X							
AE Reporting	Recorded from cycle 1 day 1 and every four weeks through 30 days after the last dose of study drug (section 7).							
Concomitant Medications	Recorded from signing of the ICF through 30 days after the last dose of study drug.							
Physical Exam	X	X			X	X	X	
Vital Signs[4]	X	X			X	X	X	
Medical History	X							
Prior antineoplastic therapies	X							
12-lead electrocardiogram (ECG)	X	As clinically indicated.						
ECOG Performance Status	X	X			X	X	X	
CBC w/ Diff and platelet count	X	X			X	X	X	
Blood Chemistry including Liver Function tests[5]	X	X			X	X	X	
PT/INR, PTT	X							
FSH, LH, Estradiol (as indicated to monitor premenopausal women per institutional standards)	X							
Pregnancy Test (Serum or Urine)[6]	X	X						

Tumor biopsy At enrollment: Archived tissue - samples are acceptable if the biopsy is no more than 18 months ago. Otherwise, a fresh sample is required prior to the study enrollment (see section 10.5.1)	X					X (Optional)		
Blood biomarker correlatives (required)		X			X (Cycle 3 Day 1 only)	X[11]	X[10]	
Tumor assessment (CT/MRI) CT or MRI of chest, abdomen and pelvis required; Skin Photography; imaging of other metastatic sites if clinically indicated.[9]	X				X Every eight weeks from C1D1 for the first 12 months (every 12 weeks after the first 12 months).	X		
RECIST Criteria -assessment	X				X	X		
^{18}F-FFNP PET/CT (Optional)[7]		X	X					
Bone scan	As clinically indicated.				As clinically indicated.			
Brain CT or MRI	As clinically indicated.				As clinically indicated.			
Fulvestrant[8]		X		X	X			
Onapristone		Continuous dosing (see section 6.0).						
Drug adherence		X			X	X		
Survival status								X

1. All screening procedures must occur within 30 days prior to enrollment.
2. If subject discontinues treatment early and/or progresses/relapses, the safety visit assessments can be completed prior to starting other therapy.
3. The safety visit will occur 30 days (+/- 14 days) from last dose of study treatment. If a subject has disease progression/relapse or subject withdrawal, then they will be followed as per follow-up requirements. Subjects will be followed every three months (±14 days) from the end of treatment visit. An alternative follow-up with either a phone call or chart review will be acceptable.
4. Include height and weight on screening. Weight, temperature, HR, RR, and BP or as per institutional standards at all timepoints.
5. No repeat laboratory evaluation and a physical exam on day 1 are required if screening completed <7 days prior to C1D1.
6. For women of childbearing potential. A negative pregnancy test must be obtained within seven to 10 days prior to the first dose of study drug(s).
7. Subjects who chose to undergo the optional ^{18}F-FFNP PET/CT for PR imaging will undergo a baseline scan at least 24 hours prior to starting treatment (no more than 7 days prior) and a follow-up scan seven to 14 days after starting treatment.
8. Fulvestrant will be given days 1 and 15 in cycle 1. The C2D1 dose should be given two weeks after C1D15 dose. Fulvestrant dosing will be every 28 days beginning with C2D1.
9. Imaging scans per section 10.1; imaging frequency (with windows) per section 10.2. Imaging at end of treatment visit not required if completed within the past 6 weeks. Skin photography required if skin lesions are present and amenable to photography.
10. If blood for correlative studies was not collected at the end of treatment visit, it should be collected at the safety visit and prior to starting any new treatment. Please refer to section 10.5.1 and 10.5.2.
11. If a research sample was drawn at Cycle 3 Day 1 and subject stopped treatment at that time, a third sample is not required.

LIST OF ABBREVIATIONS

ABCAE	advanced breast cancer adverse event
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CDK	cyclin-dependent kinases
CQ	chloroquine
CR	complete response
CRC	clinical research coordinator
CRF	case report form
CSF	cerebral spinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	cytotoxic T cell
CTO	Clinical Trials Office
DFS	disease-free survival
DLT	dose-limiting toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	data and safety monitoring plan
ER	estrogen receptor
^{18}F-FFNP	^{18}F-fluorofuranylnorprogesterone
FDA	Food and Drug Administration
GCP	good clinical practice
HCQ	hydroxychloroquine
HCT	hematocrit
HER 2	human epidermal growth factor receptor 2
HGB	hemoglobin
IP	investigational product
IRB	Institutional Review Board
LDH	lactate dehydrogenase

LMWE	low molecule weight isoforms of cyclin E
MCWCC	Medical College of Wisconsin Cancer Center
MTD	maximum-tolerated dose
NCI	National Cancer Institute
ORR	overall response rate
PBMC	peripheral blood mononuclear cells
PD	disease progression
PET	positron emission tomography
PDAC	pancreatic ductal adenocarcinoma
PK	pharmacokinetics
PR	partial response
PgR	progesterone receptor
Rb	retinoblastoma
RBC	red blood cell (Count)
ROS	reactive oxygen species
SAE	serious adverse event
SD	stable disease
SD	standard deviation
SRC	Scientific Review Committee
TMZ	temozolomide
ULN	upper limit of normal
UP	unanticipated problem
UPIRSO	unanticipated problems involving risks to subjects or others
WBC	white blood cell (count)
WON	Wisconsin Oncology Network

1. BACKGROUND

1.1 Hormone Receptor-Positive HER2-Negative Breast Cancer

Breast cancer is the most frequent cancer among women, impacting 2.1 million women each year, and causing the greatest number of cancer-related deaths among women. In 2018, it is estimated that 627,000 women died from breast cancer — that is approximately 15% of all cancer deaths among women.(1) (World Health Organization Global Health Estimates, 2019).

Estrogen-deprivation therapy is the core treatment modality in patients with hormone receptor positive (HR+, that is, estrogen or progesterone receptor, i.e., ER+ and/or PgR+) advanced breast cancer (NCCN Guidelines®).(2) Endocrine therapy options for postmenopausal women with ER+ advanced breast cancer (locally advanced, recurrent, or metastatic breast cancer (MBC)) include selective ER modulators (SERM; tamoxifen), ER antagonists (fulvestrant), selective nonsteroidal AIs (NSAI; anastrozole and letrozole) and steroidal AIs (exemestane). The cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors are rapidly transforming the care of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (HR+/HER2−) advanced breast cancer. There are currently three CDK4/6 inhibitors that have been approved by the U.S. Food and Drug Administration: palbociclib, ribociclib, and abemaciclib. It is generally recommended to use the combination of a CDK4/6 inhibitor along with an aromatase inhibitor (AI) for first-line treatment, pending OS data.(3-5) For patients with disease progression after front-line endocrine therapy, a combination of fulvestrant and palbociclib demonstrated a remarkable improvement in progression-free survival (PFS) compared with fulvestrant plus placebo in the PALOMA3 trial (median 9.5 vs. 4.6 months; HR 0.46, 95% CI 0.36-0.59).

Upon disease progression, mammalian target of rapamycin [mTOR] inhibitors plus AI based regimen is used as a second-line therapy, which can be somewhat toxic and difficult to tolerate.(6) Recent approval of alpelisib in PIK3CA-mutated hormone receptor-positive breast cancer, based on a phase III SOLAR trial of 572 patients, demonstrated a PFS of 11 months vs. 5.7 months in the alpelisib plus fulvestrant arm compared with fulvestrant alone (HR, 0.65, 95% CI 0.50–0.85).(7) However, in this trial, the benefit was noted in patients with PI3K mutations compared to those without mutations. Diarrhea and hyperglycemia were the toxicities with alpelisib. In addition, a total of 25% discontinued therapy due to toxicities, thus, emphasizing the need for novel agents. One key limitation of both the everolimus and alpelisb studies is the lack of data for the role of these agents after prior CDK4/6 inhibitor therapy.

Most patients progress on the above-mentioned treatments, and ultimately develop endocrine resistance.(8-12) While the worsening of disease is inevitable, not all patients suffer from high tumor burden, and those with oligometastatic disease, and low tumor burden continue to do well.(13) However, for patients who progress on the prior therapy with CDK inhibitors, and those who are ineligible to receive PI3K, and mTOR inhibitors due to lack of PI3K mutations, or other comorbidities, systemic chemotherapy is the only option regardless of the disease burden, and thus, novel agents as proposed in this study remain as potential options for patients with ER+/HER2- metastatic breast cancer.

1.2 The Progesterone Receptor [PgR]

1.2.1 Role of PgR in Breast Cancer Proliferation

Evidence that the PgR signaling pathway is also a major driver of breast cancer risk has continued to significantly grow during the last decade. In addition to the ER, PgR also plays a prominent role in breast cell proliferation leading to cancer progression.(14) In addition to ligand-activated

transcription, phosphorylation of PgR via growth factor-mediated kinases is associated with transcriptional hyperactivity at select phosphorylation-responsive PgR target genes that are important for breast cancer cell proliferation and pro-survival.(15)

The progesterone receptor (PR) belongs to the steroid receptor family, a subset of the nuclear receptor family, and is the mediator of progesterone action. Expressed in the human as two major forms, progesterone receptor A (PRA) and progesterone receptor B (PRB), the PR is a ligand-activated transcription factor, which plays a key role in hormonally regulated tissues, such as breast.(14-16) The PR is expressed in normal cells and in certain malignant tissues, mediating the effects of progesterone by association with a range of coregulatory 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, probably representing aggregates or clusters of multiple transcriptionally active PR-co-regulator complexes exhibiting an activated pattern (A). In the absence of ligand, PR may be distributed evenly in the nucleus in a diffuse pattern (D) [Grimm 2016]. PR foci are aberrant in cancers, being more irregular and bigger in size, suggesting that the co-regulator composition and number of complexes are altered. It is hypothesized that tumors with the A pattern (called APRpos) may benefit from onapristone treatment more than PgRpos patients with the D pattern. Studies have shown that APR is present in a significant number of postmenopausal breast and endometrial tumors.(16)

In addition to ligand-activated transcription, phosphorylation of PR via growth factor-mediated kinases is associated with transcriptional hyperactivity at select phosphorylation-responsive PR target genes that are important for breast cancer cell proliferation and prosurvival.(15) Growth factor activity may reduce or supplant the need for a progestin ligand and leads to ligand-independent activation of PR. Progesterone, but not estrogen, has emerged as a key mediator of both normal and neoplastic mammary gland stem cell expansion.(15) Consequently, the PR is considered a relevant therapeutic target for further study in breast cancer.(16-20) Activation of PR in breast cancer cells provides a strong rationale for the use of antiprogestins, in particular onapristone, that can antagonize ligand-independent and ligand-dependent PR activity for the treatment of breast cancer.

1.2.2 ESR1 Acquired Mutations Are Associated with Significant Increase in PgR Expression

Recent data suggest that mutations in the ESR1 gene encoding ERα play a major role in resistance to endocrine therapy in the clinic. The most prevalent mutations, as detected in a number of studies, are the Y537S and D538G mutations.(21) Specific acquired mutations from fulvestrant (e.g., ESR1 Y537S) are also a major driver of resistance to fulvestrant and palbociclib combination therapy.(22) These acquired mutations can lead to the expression of constitutively active ERα that can induce its downstream target genes, including PR, in the absence of estradiol.(22)

Collectively, these data suggest blocking both ER and PgR signaling pathways in patients with advanced breast cancer is an attractive yet clinically untested hypothesis. In particular, combining onapristone and fulvestrant, both full antagonists of PgR and ER, respectively, is likely to lead to complete hormonal blockade even in patients that have acquired resistance after long-term estrogen deprivation.

1.2.3 Mechanism of Action

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 PgR-dependent genes, termed progesterone response elements (PRE). The DNA-PRE binding is an energy-requiring process and is associated with chromatin remodeling.(23) A simplified diagram of the proposed mechanism of transcriptional activation of the PR is illustrated in Figure 1.

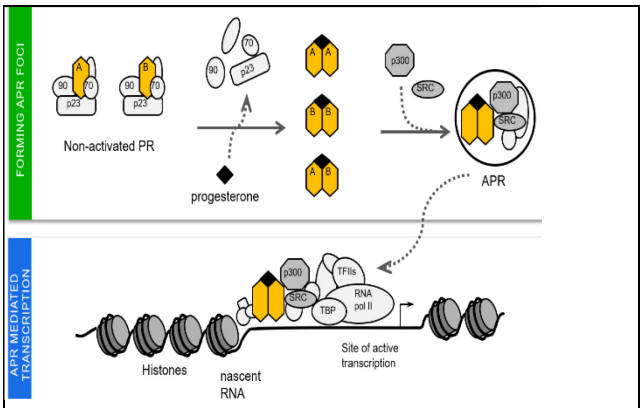


Figure 1: Proposed model of activated PR (APR) foci in transcriptional activation [Arnett Mansfield 2007]

PgR has long been considered as a mere indicator of hormonal sensitivity (i.e., to antiestrogens). In fact, PR dramatically modulates ER action in breast cancer.(24-26) It also has been demonstrated that progesterone alone was a potent stimulator of proliferation in *ex vivo* breast tumor tissue samples, while estrogen was a weak stimulator.(15)

1.2.4 PgR Isoforms and Post-Translational Modifications

The PgR 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, the proportion of PRA and PRB may be profoundly altered: PgR 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 and endometrial cancers.(20, 27, 28)

In mouse models, the knockout of PRB prevents mammary gland development(29), while the knockout of PRA prevents uterine development but has little effect on mammary gland development.(30)

PgR has numerous sites of phosphorylation, which can be induced by ligand binding but also by kinases commonly active in breast cancer, such as MAPK, CK2, and CDK2. PgR phosphorylation sites are illustrated in Figure 2. These modifications modulate the PR gene activation program in a context-dependent and ligand-specific manner: for example, phosphorylated and desumoylated PgRs recognize selected antagonists (mifepristone and aglepristone) as potent receptor agonists relative to onapristone. Thus, the PR phosphorylation profile influences its downstream

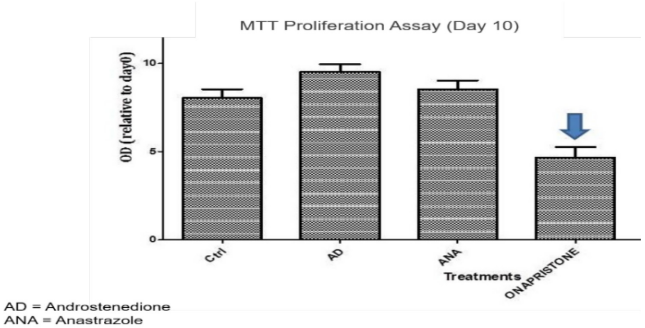


Figure 2:Onapristone activity in MCF7 tamoxifen-resistant cell line

effects and is likely to be key in a “high kinase” context, such as breast and other PR-positive cancers. Stimulation of this phosphorylation can be by MAPK, CDK, EGF or other growth factors or cytokines that activate MAPKs. pSer294 PRs induce HER2- and IGFR-associated gene sets and are required for formation of secondary mammospheres (i.e., an *in vitro* assay of cancer stem cell potential). pSer294 PR also has been implicated in regulation of PR target genes (RUNX2) required for mammary gland stem cell expansion. Phosphorylation of PR (Ser294) via growth factor-mediated kinases is associated with transcriptional hyperactivity at select phosphorylation-responsive PR target genes that are important for breast cancer cell proliferation and prosurvival.(31, 32) This property is likely key, as PR seems to be constitutively phosphorylated and activated in a subset of patients with breast cancers through abnormal activation by aberrant growth factor and kinase pathways.(31, 32) The turnover of unliganded PR in cells is roughly 20 to 22 hours, while phosphorylated PRs have a much shorter half-life, on the order of minutes to an hour when PR Ser294 is phosphorylated [Data on File]. Thus, when PR is phosphorylated and active and PR target gene products are high, such as the mRNA transcripts induced by PRs, the PR protein is often undetectable by standard Western or IHC-based protocols. This observation has key implications from both PD and diagnostic standpoints. Onapristone treatment does not permit Ser294 phosphorylation, even in the presence of progesterone. This contrasts with other antiprogestins.(15, 33, 34) Knutson et. al. concluded that “antiprogestins that block PR SER294 phosphorylation should be included ‘up-front’ as part of routine endocrine therapies for women undergoing long term management of ER+ luminal breast cancer.”(15)

In the literature, the assumption has been that in tumor tissues the PgR had no function in the absence of progesterone, and that ligand was required for PgR activation. We postulate, and stipulate that in addition to ligand-dependent activation of PgR, in a subset of breast cancer patients, PgR can also be activated in a ligand-independent manner or in the presence of low levels of endogenous ligand via phosphorylation by abnormal growth factor or kinase-type pathways. In the malignant cells, this phosphorylation of the PgR results in either a constitutively activated PgR or PgR activated by low levels of ligand; and the PgR ligand may not necessarily be nascent progesterone.

This working hypothesis does not apply to normal stromal cells, which continue to require physiologic levels of PR ligand to activate the PR-associated gene set in a ligand-dependent manner.(31, 32)

1.2.5 PR Antisense

Several animal models have shown that antiprogestins were able to inhibit tumor growth as single agents in progestin-induced, 7, 12-dimethylbenz (α) anthracene (DMBA)-induced, or estrogen-induced and even in progestin-induced but progestin-growth independent tumors. It seems that the direct antagonism of PgR is critical for growth inhibition, as shown recently with the use of PgR antisense oligodeoxynucleotides. In one study, BALB/c mice with SC 25 mm^2 mammary carcinomas expressing ERα and PR were injected intraperitoneally with PgR antisense oligos every 24 or 12 hours for five to 10 days, or continuous mifepristone SC once every 24 hours or once as an SC implant. Control mice received vehicle or scrambled oligonucleotide to PgRs. Tumor growth was inhibited by PgR antisense oligos, onapristone and mifepristone, and the authors concluded that this provided further evidence for a critical and hierarchical role for the PgR pathway in mammary carcinomas.(35, 36)

1.3 Overview of Fulvestrant

Fulvestrant is the first-in-class unique ER downregulator with no known agonist effects.(37) Fulvestrant binds, blocks and, unlike tamoxifen or other SERMs, degrades the ER, completely inhibiting ER signaling. As a result, there is less chance of the ER being activated by alternative pathways that are believed to cause resistance (e.g., growth factor-mediated mechanisms) .Fulvestrant is approved for the treatment of HR+ metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. Premenopausal women who receive ovarian suppression with GnRH analogues (leuprolide, goserelin) also can be treated with fulvestrant for metastatic HR+ metastatic breast cancer.(2) However, in postmenopausal women without symptomatic visceral disease after recurrence or progression on an AI, current clinical practice and treatment guidelines also include fulvestrant as a single agent.(2)

In postmenopausal patients who experienced progression after prior endocrine therapy (either AI or tamoxifen), fulvestrant 500 mg emerged as the optimal dose based on the results of the CONFIRM study, which showed that the higher dose (500 mg monthly) significantly prolonged PFS compared to the 250 mg dose (mPFS 6.5 vs. 5.5 months; HR= 0.80; p = 0.006).(38)

The most common clinically significant adverse reactions occurring in ≥5% of patients receiving fulvestrant 500 mg were: injection site reactions, nausea, bone pain, arthralgia, headache, back pain, fatigue, pain in extremity, hot flashes, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea, and constipation. Pooled safety analysis (SmPC) identified aspartate aminotransferase (AST), alanine aminotransferase (ALT) or alkaline phosphatase increases in approximately 15% of the treatment population with grade 3 increases seen in 1–2%. There was no difference in rates of AST, ALT, and AP elevations between groups treated with 250 mg and 500 mg doses.(39)

1.3.1 Clinical Pharmacokinetics of Fulvestrant

The recommended dose (intramuscular injection) is 500 mg at intervals of one month, with an additional 500 mg dose given two weeks after the initial dose. Fulvestrant is slowly absorbed, reaching maximum plasma concentrations after about five days. Steady state is achieved within the first month of dosing. At steady state there is more than a twofold difference between mean Cmax and Cmin. After intramuscular administration, the exposure is approximately dose proportional in the dose range of 50 to 500 mg.(39) Fulvestrant is subject to extensive and rapid distribution. Fulvestrant is eliminated mainly by metabolism. The major route of excretion is via the feces with less than 1% being excreted in the urine. Fulvestrant has a high clearance, suggesting that it is a drug with a high extraction ratio. The terminal half-life after intramuscular administration is governed by the absorption rate and was estimated to be 40 to 50 days. An *in vitro* inhibition study showed no relevant inhibition of CYP1A2, 2C9, 2C19, 2D6 or 3A4 by fulvestrant. The lack of inhibition of CYP3A4 was confirmed in an *in vivo* interaction study with midazolam. Studies using human liver preparations and recombinant human enzymes indicate that CYP3A4 is the only P450 isoenzyme involved in the oxidation of fulvestrant; however, non-P450 routes appear to be more predominant *in vivo* as interaction studies with rifampicin (CYP3A4 inducer) and ketoconazole (CYP3A4 inhibitor) demonstrated no effect on fulvestrant pharmacokinetics. The relative contribution of P-450 and non-P-450 routes *in vivo* is unknown.(39) The potential for interaction with fulvestrant therefore appears to be low. Increased exposure to fulvestrant was observed in patients with moderate hepatic impairment (Child-Pugh class B); therefore, a dose of 250 mg is recommended in these cases. Fulvestrant has not been administered to patients with severe hepatic impairment.(39)

1.4 Overview of Onapristone

Onapristone is a type I antiprogestin which prevents the PgR from dimerizing and blocks ligand-induced protein kinase-mediated phosphorylation of the PgR.(15, 34) Nondimerized PR does not bind to DNA.(20) This aspect is key to the activity of onapristone, as dimerization is necessary for binding with PREs in PR-dependent genes and subsequently with coactivators to induce transcription. In addition, onapristone blocks coactivator binding to gPR and stabilizes corepressor binding. Without functional PgR dimers and PRE binding, no PgR-dependent gene transcription can occur. Studies have been conducted to examine the ability of PgR to recruit a chromatin-remodeling complex to the promoter when bound to different classes of antagonists and the influence of this interaction on PgR dynamics and function *in vivo*.(27) contrast to mifepristone, onapristone reverses the assembly of DNA-bound PgR complexes induced by progestins.(23)

1.4.1 Non-clinical Experience

1.4.1.1 Onapristone Single-Agent Activity

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 (Figure 2) [Personal communication S Fuqua].

Onapristone also is active in T47D cell lines stimulated by either progesterone or estradiol in steroid-free serum, but not in other PgR-positive cell lines. Onapristone also blocks estradiol-stimulated growth of soft agar colony formation of tamoxifen-sensitive (MCF7L) and tamoxifen-resistant (MCF7 1GX) cells (Figure 3).(24) In their preliminary results, Lange et al. (2019, in press) found that the commercially available PR antibodies may fail to recognize phosphorylated PR, and many of these tumors will be reported as PR-, when they are actually phosphor-PR positive, where onapristone is highly active. Therefore, it is suggested that onapristone is active in both PgR+ and PgR negative tumors (2019, in press).

1.4.1.2 Methylnitrosourea-Induced Mammary Tumors

In a study of rats bearing methylnitrosourea (NMU)-induced mammary tumors, tumor-bearing animals were treated with onapristone or megestrol acetate alone or in combination with

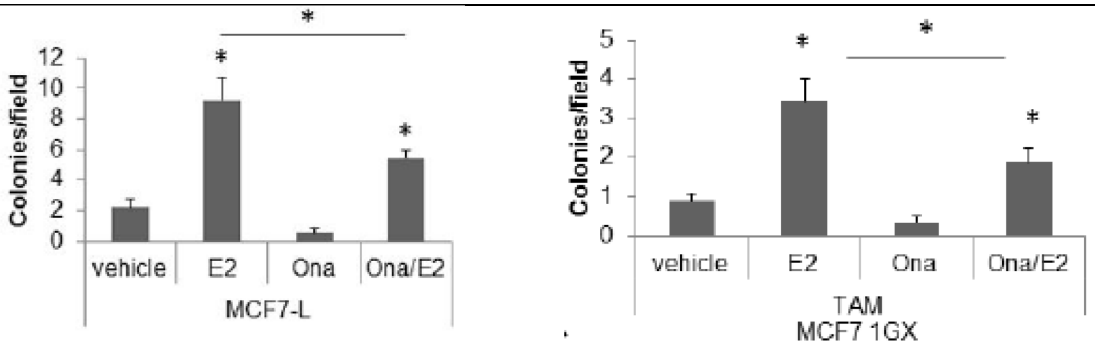


Figure 3:Onapristone blocks estradiol-stimulated growth

tamoxifen for four weeks. Monotherapy with either onapristone or tamoxifen caused partial remission of tumors in 30% of animals. When both antihormones were administered concomitantly, 80% partial and 20% complete remission were achieved, while oophorectomy induced 22% partial and 67% complete remission (see Table 1).(40)

Table 1: Remission rates of NMU-induced mammary tumors in rats treated with onapristone, tamoxifen or a combination of both antihormones

	Complete Remission (%)	Partial Remission (%)
Control	0	0
Ovariectomy	67	22
Onapristone (3 mg/kg[a])	0	30
Tamoxifen (5 mg/kg[a])	0	30
Onapristone + tamoxifen[a]	20	80

[a] *Daily SC treatment over four weeks, NMU = methylnitrosourea*

With respect to tumor growth, the combination of onapristone and tamoxifen was as effective as ovariectomy (Figure 3).(40)

Therefore, it is reasonable to hypothesize that the antitumor effect of tamoxifen may be enhanced by the combination with onapristone.(40, 41)

1.4.1.3 Non-clinical PK and Metabolism of Onapristone

The PK of onapristone has been characterized in male and female SD rats and female cynomolgus monkeys, the species used in the nonclinical safety evaluation of onapristone. Following oral dosing, onapristone showed a rapid absorption in both nonclinical species, and a moderate clearance. The systemic plasma exposure of onapristone increased in an approximately linear manner between 10 and 90 mg/kg/day in female monkeys, after 28 days of administration. In monkeys, the mean ratio of the prominent metabolite *N*-desmethyl-onapristone (M1)/onapristone $AUC_{0\text{-}t}$ ranged from 0.31 to 0.74 in the 10 to 90 mg/kg/day dose range. Overall, there was no notable sex difference in onapristone or M1 plasma exposure in rats. Renal clearance was a minor pathway of elimination for onapristone in chimeric mice. Incubation of sandwich-cultured human hepatocytes with onapristone did not reveal any significant excretion in bile canaliculi, suggesting that biliary excretion is not expected to be an important pathway of elimination in human.

Onapristone was highly protein bound in human female plasma with an unbound fraction of 0.56 ± 0.03%. Jang [1997] previously reported that onapristone does not bind to α-1-acid glycoprotein.

Twelve metabolites of onapristone were identified in rat, monkey and/or human liver microsomes. In humans, nine metabolites were observed with *N*-demethylation, mono-oxidation, and dehydrogenation as prominent metabolic pathways. None of the metabolites were unique to humans, thus, rat and monkey were appropriate toxicology test species. The chemical structures of M1 and M2 (di-*N*-demethyl onapristone) were confirmed using a reference standard. M1 formation kinetics was shown to be similar in female and male HLM.

Recombinant CYP phenotyping experiments suggested that M1 formation is predominantly mediated by CYP3A4 and CYP3A5, with minor contribution from CYP2C9. CYP3A4 and CYP3A5 were also the major isoforms responsible for the demethylation of M1 to M2. Similarly, using CYP-

specific chemical inhibitors in HLM suggested that M1 and M2 formation was predominantly mediated by CYP3A, and to a lesser extent by CYP2C8 and CYP2C9.

Onapristone did not reversibly inhibit CYP1A2 and CYP2D6. However, onapristone inhibited CYP2C8, CYP2C9 and CYP3A4, with IC_{50} values in the range of 4.3 to 30 μM. Onapristone was a time-dependent inhibitor of CYP3A4. In a pilot study, CYP1A2, CYP2B6, CYP2C and CYP3A induction was observed using hepatocytes from a human female donor.

In agreement with the high permeability and lack of efflux of onapristone in Caco-2 cells, onapristone was not a substrate of the efflux transporters MRP2, P-gp, breast cancer resistance protein (BCRP) or the bile-salt export pump (BSEP) in human hepatocytes. In addition, onapristone was not a substrate of the sinusoidal uptake transporter MRP3. Onapristone was not an inhibitor of MRP2 or BSEP. Similarly, M1 did not inhibit BSEP in human hepatocytes.

1.4.1.4 Safety, Pharmacology, and Toxicology of Onapristone

Safety pharmacology studies were conducted to identify the potential adverse effects of onapristone on several physiological systems. Central nervous system (CNS) was evaluated using Functional Observational Battery (FOB) and respiratory was evaluated using whole-body plethysmography assessment. CNS and respiratory safety pharmacology endpoints were integrated into a good laboratory practice (GLP) compliant four weeks repeat dose rat toxicology study. Cardiovascular safety pharmacology endpoints were evaluated in a GLP-compliant cynomolgus monkey study and HEK293 cells transfected with hERG.

Table 2 Summary of Safety Pharmacology Studies

Organ systems evaluated	Species / Strain	Method of admin.	Doses (mg/kg)	Gender and N per group	Noteworthy findings
VPT1140 GLP compliant **CNS**	Crl:CD(SD) rats	Oral	0 (vehicle), 10, 30 and 90 mg/kg/day (twice a day dosing at 0, 5, 15 and 45 mg/kg, 12 hours apart) for 4 weeks followed by a 2-week treatment free period.	Female 4 rats per group	No effect in the neurobehavioral parameters as measured in an FOB. A small increase in piloerection resulted in a statistically significant difference between the vehicle and mid (30 mg/kg/d) and high (90 mg/kg/day) dose. No effects observed in 10 mg/kg/day dose, except for a trend for increases in tremors, Increase in bizarre behavior was observed in some animals treated with 30 and 90 mg/kg; there was a trend for increases in tremors in all test doses; no statistically significant effect was reached in any of the doses evaluated.

Organ systems evaluated	Species / Strain	Method of admin.	Doses (mg/kg)	Gender and N per group	Noteworthy findings
Respiratory					Onapristone did not alter respiratory parameters measured in the whole-body plethysmography assessment at 10, 30, 90 mg/kg/day daily dosing.
VPT1326 GLP compliant **Cardiovascular**: Arterial blood pressure, Lead II Electrocardiography (ECG)	Monkey/ Cynomolgus	Oral	0, 10, 30 and 90 mg/kg (1 day)	Males 4/group	10 and 30 mg/kg: no effects 90 mg/kg: transient decrease in heart rate of 38 bpm at 4 hours after treatment only; QT and QTcV increase up to 37 (average 29 msec) and 30 msec (average 25 msec) respectively from 2 to 10 hours after treatment. No changes on arterial blood pressure, QRS complex, PgR and QA intervals.
VPT1318 GLP compliant Cardiac electro-physiology	in vitro test (hERG assay)	NA	Phase A: 30 µM Phase B: 1,3 and 10 µM	Groups of 3 cells/ concentration	Effect level of 10µM (4.5 µg/mL) in the hERG test was observed; indicated the potential to prolong QT No effects were present at a concentration of 3µM (1.35 µg/mL)

1.4.1.5 Genotoxicity Status of Onapristone and Metabolites

The Ames test and *in vitro* chromosome aberration assays were negative, indicating a lack of genotoxicity and mutagenicity. Earlier mouse micronucleus testing was also reported to be negative.

1.4.1.6 Clinical Experience

Onapristone (ONA) is a type I antiprogestin which prevents the PRA and PRB monomers from dimerizing, inhibits ligand-induced phosphorylation and prevents association of the PR with its coactivators, thus, preventing PR-mediated DNA transcription.(42) In contrast to other antiprogestins, ONA does not allow the PR complex to bind to DNA, minimally modulates PR-mediated genes, and inhibits ligand-induced PR phosphorylation.(33, 34) clinical anticancer activity of ONA has been previously documented in patients with hormone therapy-naïve(43) or tamoxifen-resistant(19) breast cancer (BC).

Onapristone in endocrine sensitive malignancies

More recently, an open-label, multicenter, randomized, parallel-group, phase I study (target n = 60; NCT02052128) included female patients >18 years with PR+ tumors. Fifty-two patients were randomized to five cohorts of extended release (ER) onapristone tablets 10, 20, 30, 40 or 50 mg BID, or immediate release 100 mg QD until progressive disease or intolerability. Primary endpoint was to identify the recommended phase II dose. Secondary endpoints included safety, clinical benefit and pharmacokinetics. Tumor diagnosis included: endometrial carcinoma 12; breast cancer 20; ovarian cancer 13; other 7. Median age was 64 (36–84). No dose-limiting toxicity was observed with reported liver function test elevation related only to liver metastases. The RP2D was 50 mg ER BID. Median therapy duration was eight weeks (range 2–44), and nine patients had clinical benefit lasting at least 24 weeks, including two patients with APRpos endometrial carcinoma.

In terms of safety, no dose-limiting toxicity (DLT) was observed. Only transient elevations in LFTs occurred, mostly in patients with liver metastases and abnormal LFTs at baseline. Fifty-one patients discontinued ONA treatment for disease progression, and one for an AE (bilirubin G3 elevation, eventually deemed progression of disease in the liver). Refer to section 8.2 for additional safety information.

Clinical benefit rate (partial response and stable disease lasting for at least 24 weeks) was observed in 17% of all patients including one partial response in a patient with ovarian cancer who had three prior therapies and three breast cancer patients with stable disease lasting for more than 24 weeks. These three breast cancer patients received seven, seven, and three therapies, respectively, prior to receiving onapristone and two of these patients had liver metastases.

The authors concluded that clinical benefit with excellent tolerance was seen in heavily pretreated patients with endometrial, ovarian and breast cancer.(16)

1.4.1.7 Pharmacokinetics of Onapristone

In the phase I trial(16), plasma concentrations of ONA, mono-demethylated ONA (M1) and other metabolites in plasma and urine were analyzed with a validated ultra-performance liquid chromatography with tandem mass spectrometry detection (UPLC-MS/MS) assay. Results showed that ONA AUC and Cmax were dose-proportional across dose levels, with high correlation coefficients (R2 values are 0.76 and 0.97, respectively, see Figures 5 and 6). Average Tmax was 3.01 hours (2.71–3.2) vs 1.84 hours for ER versus IR formulations, respectively, and concentrations of drug were sustained longer with a 60% (±20) relative bioavailability for ER vs IR formulation. Steady state for the ER formulation was attained before day 8, and the mean ONA minimum concentrations at steady state were up to five times those obtained at day 1; day 8 through levels were similar to day 1 for IR. There was no evidence of ONA accumulation at day 57. The observed mean t1/2 for the ER formulation was approximately 18.01 hours (range, 13.9 to 37), consistent with steady state achievement before day 8. ONA plasma concentration versus time curves suggest biphasic elimination.

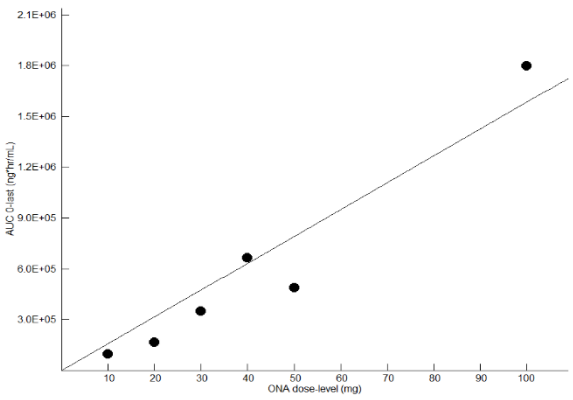


Figure 5: Onapristone AUC0-last versus first dose level

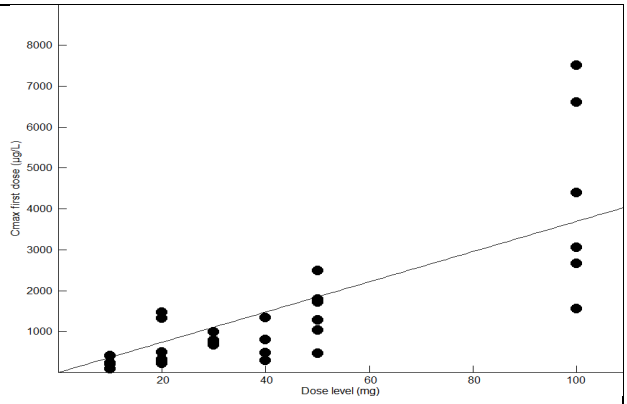


Figure 6: Onapristone Cmax versus first dose level

1.4.2 Unmet Medical Need

1. The current standard of care treatment for stage IV, HR+/HER2- recurrent/metastatic breast cancer (MBC) includes treatment with one of the cyclin dependent kinase (CDK) 4/6 inhibitors (palbociclib, ribocilcib, abemaciclib) in combination with one of the anti-estrogens as first-line therapy.(3-5) For patients with disease progression after front-line endocrine therapy, the fulvestrant plus palbociclib combination demonstrated a remarkable improvement in progression-free survival (PFS) compared with fulvestrant plus placebo in the PALOMA3 trial (median 9.5 vs. 4.6 months; HR 0.46, 95% CI 0.36-0.59).(3, 44, 45)
2. Upon disease progression, PI3 kinase /mTOR inhibitors are used in combination with endocrine therapy as the second-line regimen for disease progression.(6) Recently, alpelisib, a PI3Kinase inhibitor, was approved in combination with fulvestrant for PI3Kinase-mutated tumors, based on the SOLAR-1 trial data. This trial also reported a small cohort of patients who achieved a 15% RR with prior exposure to CDK4/6 inhibitor therapy.(7) Hyperglycemia, and diarrhea were main side effects of alpelisib, and 25% of the study patients discontinued alpelisib due to adverse effects.(7) Despite the promising data, both everolimus and alpelisib have concerning side effects, and are somewhat toxic and difficult to tolerate due to pulmonary toxicity, and hyperglycemia (4). While there are no approved treatments for anti-PgR-based regimens beyond progression on CDK4/6 inhibitors, it is anticipated that treatment with antiprogesterone agents, such as onapristone, may overcome the drug resistance due to the ESR mutations that develop over the time.(12)
3. Regardless, most patients progress on these agents, and ultimately develop endocrine resistance. While the worsening of disease is inevitable, not all patients suffer from high tumor burden, and those with oligometastatic disease, and low tumor burden continue to do well.(13) However, for patients who progress on the prior therapy with CDK inhibitors, PI3K, and mTOR inhibitors, systemic chemotherapy is the only option regardless of the disease burden, thus, emphasizing the critical need for novel treatments. Exploring later lines of therapy, previous trials utilizing single-agent tamoxifen reported a 10% ORR.(46) Everolimus plus exemestane in the second-line setting led to an ORR of 9.5% in the combination arm, compared to exemestane alone (0.4%)(6) In patients who had three prior lines of therapy, single-agent abemaciclib provided 20% response rates, median PFS six months (Monarch 1).(47) Therefore, based on these trials' data, the proposed study with a combination of onapristone plus fulvestrant may be considered promising for further study if an ORR of 20% is identified in patients with prior treatment with CDK4/6 inhibitors-based regimens.

1.5 Overview of Progesterone Receptor Imaging

Tumoral expression of PgR can be visualized and quantified through the use of a radiolabeled progestin, ^{18}F-fluorofuranylnorprogesterone (^{18}F-FFNP), and positron emission tomography/computed tomography (PET/CT) imaging (48-53). A “first-in-human” study involving 20 patients with invasive breast cancer has been published using FFNP-PET/CT imaging.(54) There were no adverse events, changes in vital signs, laboratory values or electrocardiograms, or clinically detectable pharmacologic effects. Dosimetry evaluation determined that the effective dose equivalent of ^{18}F-FFNP is comparable to other clinically utilized PET imaging agents. ^{18}F-FFNP uptake was greater in PR+ cancers compared to PR- cancers. Thus, ^{18}F-FFNP PET appears to be a feasible method of imaging PgR in breast cancer patients.(48-54)

2 HYPOTHESIS AND OBJECTIVES

Table 3 Objectives and Endpoints

Objective	Endpoint
Primary	
Estimate the objective response rate (ORR).	Best overall response of CR or PR, as per RECIST 1.1.
Secondary	
To evaluate progression-free survival rate (PFS).	Time from date of enrollment to the date of first documented disease progression or death due to any cause.
Estimate the disease control rate (DCR).	Best overall response of CR, PR or SD lasting for ≥ 24 weeks, as per RECIST 1.1.
To describe time to response and duration of response.	Time to response: Time from enrollment to first documented response (CR or PR). Duration of response: Time between the first date of documented response to progression or death due to breast cancer.
To evaluate the safety and tolerability.	Type, frequency and severity of adverse events and laboratory abnormalities according to CTCAE version 5.0.

3 STUDY DESIGN

3.1 General Description

A phase II single-arm trial of onapristone in combination with fulvestrant for women and men with ER-positive, PgR-positive or negative and HER2-negative locally advanced or metastatic breast cancer after progression on aromatase and CDK4/6 inhibitors. The study will enroll up to 39 patients.

3.2 Estimated Time for Study Completion

3.2.1 Primary Completion

The study will reach primary completion in approximately 36 months from the time the study opens to accrual.

3.2.2 Study Completion

The study will reach study completion 48 months from the time the study opens to accrual.

4 SUBJECT SELECTION

4.1 Checklist. Use the below checklist to confirm a subject's eligibility. For each subject, this checklist must be completed and maintained in the subject's chart.

4.2 Eligibility Criteria

No waivers of protocol eligibility will be granted. When clinical factors relating to an eligibility item are unclear or questionable, the study PI or study chair (Kari Wisinski kbwisinski@medicine.wisc.edu or Sailaja Kamaraju, skamaraju@mcw.edu) can only provide guidance or clarification on eligibility.

Enrolling investigator to initial next to each eligibility criteria.

Inclusion Criteria

Each subject must meet all the following inclusion criteria to be enrolled in the study:

_____ 1. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.

_____ 2. Men and women with advanced ER+, (PgR positive or negative), and HER2 negative breast cancer. Advanced is defined as locally advanced or locoregionally recurrent or metastatic and not amenable to curative therapy.

_____ 3. Below-mentioned prior lines of therapy are allowed in the adjuvant and or metastatic HR+/HER2- setting.

- Patients must have had prior endocrine therapy either in the adjuvant or metastatic setting (SERM (tamoxifen, raloxifene, toremifene) or any of the aromatase inhibitors (anastrozole, letrozole, exemestane), or oral SERD on a clinical trial, either in the adjuvant or metastatic setting (but not prior exposure to fulvestrant)
- Patients must have received prior therapy with oral CDK4/6 inhibitors in the metastatic setting.
- Other standard therapies in the metastatic setting (such as mTOR inhibitors) are allowed

- Patients who previously received any one of the standard adjuvant chemotherapy regimens in a curative setting are eligible for this study.
- One line of prior chemotherapy in the metastatic setting is allowed (i.e. any single agent or doublet cytotoxic chemotherapy, not limited to xeloda).

_____ 4. Histologically and/or cytologically confirmed diagnosis of ER+, PgR+/- and HER2- breast cancer by local laboratory at diagnosis of metastatic disease. Hormone receptor positivity is defined as ER and PgR positivity in at least 1% cells by immunohistochemistry (IHC). HER2-negative breast cancer is defined as a negative *in situ* hybridization test or an IHC status of 0, 1+ or 2+. If IHC is 2+, a negative *in situ* hybridization (FISH, CISH, or SISH) test is required.

_____ 5. Measurable disease, i.e., at least one measurable lesion, as per RECIST 1.1 criteria. A palpable, and measurable breast mass is acceptable.

_____ 6. ECOG Performance status ≤ 2. ECOG PS: _____ Date: _____

_____ 7. Adequate organ function:

- AST, ALT ≤ 2.5 times institutional upper limit.

  AST: _____ ULN: _____ Date: _____

  ALT: _____ ULN: _____ Date: _____

- Total bilirubin ≤ 1.5 × ULN, except for subjects with Gilbert's syndrome who may be included if their total bilirubin is ≤ 3.0 × ULN and direct bilirubin ≤ 1.5 × ULN.

  T. Bili: _____ ULN: _____ Date: _____

  If subject has Gilbert's syndrome:

  D. Bili: _____ ULN: _____ Date: _____

- ALP ≤ 2.5 times institutional upper limit with exception that ALP of < 5 x ULN is acceptable in patients with elevated with ALP due to bone metastases (in the absence of liver metastases).

  ALP: _____ ULN: _____ Date: _____

- Serum creatinine <1.5 × ULN.

  Creatinine: _____ ULN: _____ Date: _____

- Absolute neutrophil count (ANC) ≥1000/μL.

  ANC: _____ Date: _____

- Patients with lymphopenia are eligible at the discretion of the treating provider.

- Hemoglobin (Hb) ≥ 8g/dL.

  Hemoglobin: _____ Date: _____

- Platelet count ≥ 100,000/μL.

  Platelets: _____ Date: _____

_____ 8. Female subjects must meet one of the following:
- Postmenopausal for at least one year before enrollment,
  OR
- Surgically sterile (i.e., undergone bilateral oophorectomy),
  OR
- Premenopausal is defined as someone who has had menses at any time in the preceding 12 months. Premenopausal women who are eligible for this trial will require a GnRH analogue and treating physician may choose to monitor the ovarian function with laboratory tests (FSH/LH/Estradiol) to ensure a complete menopausal status with cessation of menses.

_____ 9. Women of childbearing potential must have a negative pregnancy test within seven days of registration. Subjects must have a negative pregnancy test seven to 10 days prior to starting study treatment.

Date of negative pregnancy test: _____

_____ 10. An FFPE tumor biopsy block or up to 20 superplus frost slides with unstained histological sections at 4 micrometer thickness are required at the time of study entry. Archived tumor tissue acceptable (metastatic disease from non-bone and non-brain sites preferred, but primary breast or lymph node tissue is permitted) if obtained in the 18 months prior to study registration, otherwise a fresh biopsy will be required if deemed safe by the treating physician (minimal risk to patient) (see section 10.5.1). Confirmation of adequate and available tissue sample is to be determined by the site's pathologist. Tumor samples do not need to be shipped for eligibility purposes. Tumor samples do not need to be shipped until subject is confirmed eligible and is registered for treatment.

_____ 11. Ability to take oral medications (without crushing). Please refer to section 6.1.2 for directions on taking the study drug (onaprisone).

_____ 12. To participate in the optional ^{18}F-FFNP PET/CT imaging, the subject must have ER positive, HER2 negative, AND PgR positive disease and at least one extra hepatic lesion measuring at least 10 mm in size.

Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

_____ 1. Prior treatment with an anti-progesterone agent.

_____ 2. Prior treatment with fulvestrant in the metastatic setting.

_____ 3. Prior treatment with CDK4/6 inhibitors in the neoadjuvant/adjuvant setting.

_____ 4. History of malignancy other than breast cancer within three years prior to registration except for adequately treated non-melanoma skin cancer, cervical carcinoma *in situ*.

_____ 5. History or presence of clinically active, and symptomatic CNS metastasis: If the patient fulfills the following criteria, they will be eligible for the trial:

- Completed prior therapy (including radiation and/or surgery) for CNS metastases ≥ 28 days prior to the start of study treatment and CNS tumor is clinically stable at the time of screening and patient is not receiving steroids and/or enzyme inducing anti-epileptic medications for brain metastases.

_____ 6. Subjects with any of the following conditions:

- Clinically significant illness or systemic disease as determined by the treating physicians.
- Active hepatitis or uncontrolled infection or any other clinically significant cirrhosis or other disease that, in the opinion of the investigator would pose a risk to subject safety or interfere with the study evaluation, procedures or completion. Testing for infectious hepatitis is not required for the study. Treating provider may choose additional testing if indicated clinically.

_____ 7. Patients who have had systemic chemotherapy, or targeted therapy, within two weeks prior to starting study treatment or those who have not recovered from acute effects of any prior therapy to baseline or Grade ≤1. Grade 2 or higher exceptions include alopecia, up to grade 2 neuropathy or other grade 2 AEs or lab values not constituting a safety risk in the opinion of the treating physician. NCI CTCAE v5.0 will be used

_____ 8. Co-administration with any prescriptions during the four weeks prior to first onapristone dosing and concerns for possible drug interactions should be discussed with the pharmacist. Please review Table 6 for additional details.

_____ 9. Patients who are pregnant or breast feeding.

_____ 10. History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) or symptomatic pericarditis within 6 months prior to registration.

_____ 11. Symptomatic congestive heart failure (New York Heart Association III-IV).

_____12. Clinically significant cardiac arrhythmias (e.g. ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g. bifasicucular block, Mobitz type II and third-degree AV block).

_____13. Any episode of atrial fibrillation in the prior 12 months.

_____14. QT interval >480 msec.

_____15. Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome.

_____16. Concomitant use of medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe that cannot be discontinued (within 5 half-lives or 7 days prior to starting study drug) or replaced by safe alternative medication.

_____17. Systolic blood pressure (SBP) > 160 mmHG or <90 mmHg at screening.

"I have reviewed all inclusion and exclusion criteria and confirm the subject is eligible."

_____ _____
(CRC Signature) (Date)

_____ _____
(Investigator/Enrolling Physician Signature) (Date

5. STUDY ENTRY AND WITHDRAWL

5.1 Required Preregistration Screening Tests and Procedures

The study-specific assessments are detailed in this section and outlined in the Study Calendar of Events. Screening assessments must be performed within 30 days prior to registration. Any results falling outside of the reference ranges may be repeated at the investigator's discretion. Visit procedures that were performed as standard of care prior to consent (without the specific intent to make the subject eligible for the trial), may count toward screening tests and eligibility if they are within the screening window.

A written, signed informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A signed ICF copy will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All WON sites under the purview of their local IRBs follow recruitment and consent processes approved by the local IRB of record. WON sites for which UW HS-IRB is serving as the IRB of record, will follow recruitment and consent process approved by UW HS-IRB. Documentation of both the informed consent process and that the process occurred prior to a subject's entry into a WON study is recorded in the subject's source documents.

All subjects who agree to participate and provide written informed consent and HIPAA authorization will be registered in OnCore®, the UWCCC and WON Cancer Center Clinical Trial Management System. The system is password protected and meets HIPAA requirements.

5.2 Registration Process

Patients must not start protocol treatment prior to registration.

Research personnel at WON sites who enter data into OnCore® must have completed human subjects training and Health Insurance Portability and Accountability Act (HIPAA) training.

At the time of registration, the following will be required and verified by (UWCCC):

- Subject eligibility
- Signed informed consent form
- Signed HIPAA authorization form

Refer to the Study Operations Manual for additional details regarding registration and eligibility verification.

5.3 Discontinuation of Study Treatment, Withdrawal, and Compliance

Discontinuation from the study treatment does not mean discontinuation from the study. Subject will be considered in follow-up, study procedures should still be completed as indicated by the study protocol, and AEs/SAEs will continue to be reported according to this protocol.

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

- Disease progression.
- General or specific changes in the subject's condition renders the subject unacceptable for further treatment in the investigator's judgment.
- Intercurrent illness that prevents further treatment administration.
- Subject decides to withdraw from the study.
- The subject has significant noncompliance with the protocol (see below).
- Unacceptable adverse event(s) and/or dose level reduction beyond requirements as detailed in this protocol.
- Study stopping rules are met.

Subjects who sign the informed consent form, enroll, and receive the study intervention, but subsequently withdraw, or are withdrawn or discontinued from the study will not be replaced.

5.3.1 Consent Withdrawal

A subject may decide to withdraw from the study at any time by informing the study principal investigator or the site study team.

If a subject intends on withdrawing consent, staff should confirm which of the following options the subject chooses and document the discussion:

- Full consent withdrawal with no study follow-up.
- Selective consent withdrawal from interventional portion of the study but agrees to continued follow-up of associated clinical outcome information.

5.3.2 Investigator-Initiated Withdrawal

The investigator will withdraw a subject whenever continued participation is no longer in the subject's best interests. Reasons for withdrawing a subject include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a subject's request to end participation, a subject's noncompliance or simply significant uncertainty on the part of the investigator that continued participation is prudent. The reason for study withdrawal and the date the subject was removed from the study must be documented.

Subjects withdrawn from study treatment will be asked to return for a 30-day follow-up visit, and future appointments are at the discretion of the treating provider, but not required beyond 30 days per the study guidelines.

Withdrawal Documentation Procedure: The reason for study withdrawal and the date the subject was removed from the study must be documented in the case report form.

5.4 Lost to Follow-Up

The following actions must be taken if a participant fails to return to the clinic for a required study visit and/or is unable to be reached for follow-up:

- The investigator or designee must make every effort to regain contact and/or reschedule a missed visit with the subject.
- A subject is deemed lost to follow-up if his/her status cannot be obtained after all of the following occurs at two consecutive scheduled protocol calendar time points:
    - Three telephone calls (at least one day apart) from the study team are unanswered,
      AND
    - A letter to the subject's last known mailing address goes unanswered,
      AND
    - These contact attempts must be documented in the subject's medical record or study file.
- Update OnCore® (follow-up tab and eCRF) when a subject is officially considered lost to follow-up.
- If a subject is considered lost to follow-up, but subsequently contacts the study team, the subject should be considered in follow-up again.

5.5 End of Study Definition

A subject is considered to have completed the study if he or she completes all phases of the study, including the last visit or the last scheduled procedure shown in the calendar of events or is discontinued.

5.6 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause (as determined by the study PI, DSMC, sponsor, and/or IRB). Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator (PI) will promptly inform the Institutional Review Board (IRB), and the sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes.

6 TREATMENT PLAN

6.1 Investigational Agent Administration

All patients will receive onapristone 50 mg by mouth twice (BID) daily and fulvestrant (500 mg) intramuscular injection on cycle1 days 1 and 15, then, 500 mg once monthly until progression beginning with cycle 2 day 1. There will be no breaks between dosing cycles. A complete cycle of treatment is defined as 28 days. All dosages prescribed and dispensed to the subject and all dose changes during the study must be recorded on the CRF.

Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

6.1.1 Fulvestrant

Fulvestrant dose of 500 mg (or two injections of 250 mg each) will be used. For information on fulvestrant and management of related AEs refer to the Faslodex® prescribing information. Fulvestrant will be procured locally according to local practice and regulation. Fulvestrant (500 mg) intramuscular injection will be administered on days 1, 15 (cycle 1), then two weeks later (cycle 2, day1), then once every 28 days thereafter.

6.1.2 Onapristone

The dose of onapristone will be 50 mg twice daily (BID). Context Therapeutics or its designee will provide onapristone as coated tablets of 20 mg and 10 mg strength to allow for dose modification for management of adverse events in bottles of 60 tablets each. The storage conditions for the onapristone will be described on the medication label. Medication labels will comply with the legal requirements in the United States.

The investigator should instruct the subject to take the study drugs as per protocol and drug accountability must be performed on a regular basis. Subjects will be instructed to return unused study drugs and empty containers to the site at the end of each cycle. Subjects will be given a pill diary to track onapristone dosing and will be instructed to return the diary at their next clinic visit along with all pill bottles (including empty bottles). Site personnel will review the diary with each subject to evaluate adherence to the dosing schedule.

All dosages prescribed and dispensed to the subject and all dose changes during the study must be recorded on the CRF. The following general guidelines should be followed for onapristone administration:

Subjects should be instructed to take onapristone twice daily every 12 hours, and the dosing is independent of food intake. For any missed doses, subjects are allowed a 4 hour window, and any dose missed by more than 4 hours should not be taken (at least 8 hours between doses). For example, if the first dose is taken at 6 am, the evening dose will be at 6 pm. If the morning dose is missed, they can take onapristone up until 10 am and skipped doses aren't allowed after 10 am. If the subject ends up taking the morning dose at 10 am (instead of 6 am), the subject can take the evening dose at 6 pm as originally planned, and get back to the regular schedule starting the next day.

Onapristone should be taken with a glass of water. Subjects should swallow the tablet as a whole and not chew or crush them. If vomiting occurs during the course of treatment, no redosing of the subject is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted in the adverse events section of the CRF.

6.1.3 ^{18}F-FFNP

^{18}F-FFNP is an investigational radiopharmaceutical used with PET/CT for visualizing PR-rich target tissues and quantifying available PR-binding sites. It is given in a tracer dose amount for imaging purposes. The compound is not a therapeutic agent.

If funding is secured and workflows are in place, the optional PET/CT scans will be performed at UWCCC and may also be performed at other WON sites participating in the Wisconsin Oncology Network of Imaging eXcellence (WONIX).

The optional PET/CT will be completed at least 24 hours prior to C1D1 (no more than 7 days prior) and repeated 7 to 14 days after C1D1. Prior to arrival, the subject should be well-hydrated and does not need to be fasting.

Upon arrival, the subject's height, weight, and vital signs (blood pressure, heart rate, respiratory rate, and temperature) should be recorded. The subject will have an intravenous line placed (e.g., 20 g, antecubital vein), typically in the arm opposite to the side of primary breast cancer or side of prior axillary lymph node surgery.

The dose of the investigational imaging agent, ^{18}F-FFNP, is approximately 7 mCi (259 MBq), IV slow infusion over approximately two minutes followed by saline flush. The injection site will be inspected by the technologist to assess for any possible infiltration.

Vital signs (blood pressure, heart and respiratory rate, and temperature) will be taken after injection. The subject will wait approximately 60 minutes to allow for biodistribution and tumor uptake of the radiopharmaceutical prior to imaging. The subject should void immediately prior (five to 10 minutes) to image acquisition. Vital signs (blood pressure, heart and respiratory rate, and temperature) will be taken after the imaging acquisition is complete. Subjects will be contacted by site personnel to evaluate for adverse events occurring in the 24 hours following the PET/CT scan. This can be done via a telephone call at least 24 hours, but not more than 72 hours after the completion of the PET/CT scan.

Supportive Care

During the study period, blood transfusions, bone-modifying agents for bone metastases, radiation, and other supportive care measures (i.e., growth factor support, physical therapy, lymphedema therapy, acupuncture) are allowed for symptom control.

Patients are allowed to continue the study treatment during radiation if agreeable to the treating provider. New symptoms, such as pain, are not considered disease progression, and patients are allowed to be on the study treatment unless/until there is a clear disease progression on imaging.

6.2 Dose Modification

6.2.1 Dose Modification of Fulvestrant

During the study period, dose modifications of fulvestrant are allowed as decided by the treating physician.

6.2.2 Dose Modification of Onapristone

In the preliminary studies, there were no grade 4 adverse effects (AEs) reported with a single dose of onapristone (10 mg immediate release (IR)) in healthy female volunteers. The treatment doses of onapristone (10–50 mg extended release BID or 00 mg /day) in patients with prostate cancer, breast, ovarian and endometrial cancers also demonstrated no grade 4 toxicities. The majority of the adverse toxicities were related to asthenia (16%), GGT increase (15%), nausea (14%), increased AST (12%), and increased ALT (11%).Two subjects discontinued onapristone due to AEs, and one patients discontinued due to unrelated AEs (cytopenias) due to marrow involvement of the disease secondary to bone metastases. One patient had 25% dose reduction due to liver toxicity, and ultimately discontinued onapristone due to diseases progression and LFT abnormalities. One death was reported within 30 days of discontinuation of onapristone due to

respiratory distress related to progressive lung metastases. Based on this available data under the Context Therapeutics development program, no major adverse effects are anticipated from onapristone, and the table below provides additional guidelines for dose modifications.

Management of severe or intolerable adverse reactions at least possibly, probably or definitely related to onapristone requires dose reduction, temporary interruption, and/or discontinuation of onapristone therapy. A maximum of two dose reductions will be allowed, at which point the patient will be allowed to continue treatment at that reduced dose for the following cycles. Any adverse events even after the dose reductions will indicate treatment discontinuation with onapristone. Dose reduction should be based on the worst preceding toxicity. Please refer to Tables 4, and 5 for guidance.

Table 4 Dose Reduction Steps for Onapristone

Dose level	Dose and schedule	Number of tablets and strength
Starting dose	50 mg BID continuously	2 × 20 mg tablet and 1 × 10 mg tablet
Dose level 1	40 mg BID continuously	2 × 20 mg tablet
Dose level 2	30 mg BID continuously	1 × 20 mg tablet and 1 × 10 mg tablet

Recommendations for dose reduction or interruption of onapristone in the management of adverse reactions are summarized in Table 5. Clinical judgment of the treating physician, including confirmation of lab values (by means of retesting as deemed necessary), should guide the management plan of each subject based on individual benefit/risk assessment.

Once the onapristone dose has been reduced, no re-escalation will occur, even upon resolution of the AE. If a subject requires a dose delay of onapristone for > 28 days from the intended day then the subject must be discontinued from onapristone but may continue fulvestrant.

Table 5 Criteria for Dose Modification of Onapristone Treatment

Adverse event	**Dose of Onapristone**
Hematological*	
Neutropenia (ANC)	
Grade 1 (< LLN - 1.5 × 10^9/L)	Maintain dose level.
Grade 2 (< 1.5–1.0 × 10^9/L)	Maintain dose level.
Grade 3 (< 1.0–0.5 × 10^9/L)	
First occurrence	Dose interruption until ANC ≥ 1.0 × 10^9/L ; when improved, resume and reduce by one dose level.
Second occurrence	Dose interruption until ANC ≥ 1.0 × 10^9/L ; when improved, resume and reduce by one dose level.
Third occurrence	Discontinue onapristone and continue fulvestrant at the discretion of treating physician.
Grade 4 (< 0.5 × 10^9/L)	Discontinue onapristone and continue fulvestrant at the discretion of treating physician.

Adverse event	Dose of Onapristone
Febrile neutropenia: ANC < 1.0 × 10^9/L, with a single temperature of ≥ 38.3 °C or a sustained temperature of ≥ 38 °C for more than one hour.	First or second episode: Dose interruption until resolved until ANC ≥ 1.0 × 10^9/L ; when improved and afebrile, resume and reduce by one dose level. Third episode of febrile neutropenia: Discontinue onapristone and continue fulvestrant at the discretion of treating physician.
Thrombocytopenia (PLT)	
Grade 1 (<LLN - 75 × 10^9/L)	Maintain dose level.
Grade 2 (<75–50 × 10^9/L)	Maintain dose level.
Grade 3 (<50–25 × 10^9/L)	
First occurrence	Dose interruption until platelets count is ≥75,000, then resume and reduce by one dose level.
Second occurrence	Dose interruption until the platelet count is ≥75,000, then resume and reduce by one dose level.
Third Occurrence	Discontinue onapristone and continue fulvestrant at the discretion of treating physician.
Grade 4 (< 25 × 10^9/L)	Discontinue onapristone and continue fulvestrant at the discretion of treating physician.
Laboratory	
Serum creatinine	
Grade 1 (≤1.5 × ULN)	Maintain dose level.
Grade 2 (>1.5–3 × ULN)	Hold, evaluate for other causes. If the workup is negative, and creatinine resolved to ≤1.5XULN within 14 days, resume and consider maintaining the dose level but may reduce by one dose level.
Grade 3 (>3.0–6.0 x ULN)	Hold, evaluate for other causes. If related to onapristone, then permanent discontinuation of treatment. If not related, and the creatinine level improves to ≤1.5XULN within 14 days, then resume at same dose level. If renal dysfunction is related to onapristone and or >14 days required for recovery, then discontinue onapristone and continue fulvestrant at the discretion of the treating physician.
Grade 4 (>6.0 x ULN)	Hold, evaluate for other causes. If related to onapristone, then permanent discontinuation of treatment. If not related, and the creatinine level improves to ≤1.5XULN within 14 days, then resume at same dose level. If renal dysfunction is related to onapristone and or >14 days required for recovery, then discontinue onapristone and continue fulvestrant at the discretion of the treating physician.
Total bilirubin**	
Grade 1 (> ULN - 1.5 × ULN)	Maintain dose level.

Adverse event	Dose of Onapristone
Grade 2 (> 1.5–3.0 × ULN)	Dose interruption. Evaluate for other causes, and repeat LFT every week until resolved to ≤ 1.5 x ULN. – If resolved in ≤14 days, maintain dose level. – If resolved in >14 days, then resume and reduce by one dose level.
Grade 3 (> 3.0–10.0 × ULN) **	Dose interruption. Evaluate for other causes, and repeat LFT every 72 hours until resolved to ≤ 1.5 × ULN. – If resolved in ≤14 days, then resume and reduce by two dose levels – If resolved in >14 days, discontinue onapristone and continue fulvestrant at the discretion of treating physician.
Grade 4 (> 10.0 × ULN) **	Discontinue onapristone and continue fulvestrant at the discretion of treating physician.
Liver function tests (ALT or AST)	
Grade 1 (> ULN – 3.0 × ULN)	Maintain dose level.
Grade 2 (>3.0–5.0 × ULN)	Dose interrupt, and evaluate for other causes, and repeat LFT every week until resolved to ≤ 3.0 x ULN. If resolved in ≤14 days, maintain dose level. If resolved in >14 days, then resume and reduce by one dose level
Grade 3 (> 5.0–20.0 × ULN)	Dose interruption. Repeat LFT every 72 hours until resolved to < or equal to grade 1 value. – If resolved in ≤14 days, then resume and reduce by one dose level. – If resolved in >14 days, may resume with reducing two dose levels and monitoring of LFTs twice a week for the first week and then weekly for four weeks (then return to study calendar).
Grade 4 (> 20.0 × ULN)	Discontinue onapristone and continue fulvestrant at the discretion of treating physician.
Hy's Law Criteria	
Grade ≥ 2 bilirubin in conjunction with grade ≥2 transaminase and without elevation of alkaline phosphatase)	Discontinue onapristone and continue fulvestrant at the discretion of treating physician.
Other non-hematological toxicity* **	
Grade 1	Maintain current dose.
Grade 2	Continue unless intolerable despite optimal medical management, then dose interruption. Monitor toxicity until resolved to grade 1 or tolerable grade 2. If grade 2 event was tolerable to subject, the study treatment could continue under the supervision of the treating provider.

Adverse event	Dose of Onapristone
	– If resolved in ≤14 days, maintain dose level. – If resolved in >14 days, then resume and reduce by one dose level.
Grade 3	Dose interruption. Monitor toxicity until resolved to grade 1 or better. <u>First Occurrence</u> – If resolved in ≤14 days, maintain dose level. – If resolved in >14 days, then resume and reduce by one dose level. <u>Second Occurrence</u> Dose interruption. Monitor toxicity until resolved to grade 1 or better. – If resolved in ≤14 days, maintain dose level. – If resolved in >14 days, discontinue onapristone and continue fulvestrant at the discretion of treating physician. <u>Third Occurrence</u> - Discontinue onapristone and continue fulvestrant at the discretion of treating physician.
Grade 4	Discontinue onapristone and continue fulvestrant at the discretion of treating physician.

*No dose modifications planned for other hematologic parameters (i.e., lymphocytes).
**For patients with Gilbert Syndrome, these dose modifications apply to changes in direct bilirubin only.
***Dose modifications for nausea, vomiting, diarrhea or electrolyte abnormalities only required if toxicity lasts longer than 48 hours despite maximal medical therapy. Treating providers may choose to evaluate subjects with pertinent labs for further evaluation (for fatigue, only if toxicity lasts longer than seven days despite maximal medical therapy).

Potential for Drug-Drug Interaction

In vitro, onapristone is a reversible as well as a time-dependent inhibitor of CYP3A4 and showed potential for CYP3A4 induction. 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 6).

Inhibitors of CYP3A4: Coadministration with strong inhibitors of CYP3A4 should be avoided. Coadministration with moderate CYP3A4 inhibitors should be used in caution. Seville orange, star fruit, grapefruit and their juices affect P450. Concomitant use should be avoided.

Inducers of CYP3A4: Avoid the use of strong CYP3A4 inducers. If patients require coadministration of strong CYP3A4 inducers (i.e., phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's wort), treating providers and the designated pharmacists are required to monitor patients' labs given that there are no clinical data to guide dose adjustment for onapristone in patients receiving strong CYP3A4 inducers or inhibitors.

Table 6: Clinically relevant drug interactions: inducers and inhibitors of isoenzyme CYP3A. Treating providers may choose to use the reference link below for drug interactions.

Inducers Barbiturates, carbamazepine, enzalutamide, glucocorticoids, modafinil, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, troglitazone, efavirenz, nevirapine.
Strong inhibitors Clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin.
Moderate inhibitors Aprepitant, diltiazem, erythromycin, fluconazole, grapefruit juice, verapamil.
Indiana University School of Medicine's Drug Interaction Table (https://drug-ineteractions.medicine.iu.edu/Main-Table.aspx (accessed on March 1, 2019)

6.2.3 Dose Modification of ^{18}F-FFNP

No dose modification of ^{18}F-FFNP is planned in this study.

6.3 Dietary Restrictions

None.

6.4 Monitoring Subject Compliance

Study drug will be administered or dispensed only to eligible subjects under the supervision of the investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing. Comprehensive instructions will be provided to the subject in order to ensure compliance with dosing procedures. The subject will be requested to maintain a medication diary of each dose of medication. The medication diary and all study drug containers will be returned to clinic staff at the end of each cycle.

6.5 Follow-Up Period

Subjects will be followed for one year after removal from the study treatment or until death, whichever occurs first.

7 ADVERSE EVENTS: DEFINITIONS, COLLECTION AND REPORTING REQUIREMENTS

7.1 Definitions

7.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. (International Conference on Harmonization [ICH], E2A, E6).

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, located on the CTEP web site:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures.

7.1.2 Serious Adverse Event (SAE)

Serious Adverse Event (SAE) means any untoward medical occurrence that results in any of the following outcomes:

- **Death.** Results in death.

- **Life threatening**. Is life threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).

- **Hospitalization**. Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification in the paragraph below on planned hospitalizations).

- **Disability/incapacity**. Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).

- **Pregnancy**

- **Medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

7.1.3 Attribution of an Adverse Event

Attribution is an assessment of the relationship between the AE and the medical intervention.

Relationship Assessment: In-Depth Definitions

For all collected AEs, the clinician who examines and evaluates the subject will determine the adverse event's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below:

Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-

challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.

Probably Related: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.

Possibly Related: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events). Although an adverse drug event may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

Unlikely: A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).

Unrelated: The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

7.1.4 Expectedness of an Adverse Event

Study investigator or treating physician will be responsible for determining whether an AE is expected or unexpected as indicated in the protocol, informed consent form and/or drug information brochure. 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 study intervention.

7.2 Collection and Reporting Requirements for Adverse Events and Serious Adverse Events

7.2.1 Collection of Adverse Events

All (or specify if only certain grade AE needed) adverse events (including SAEs) must be recorded in OnCore® and an adverse event log. All AEs required to be collected must be graded according to the CTCAE v5. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. Investigator's or treating physician's assessment of AE attributions must also be documented.

AEs will be collected from the time the subject signs the consent form through 30 days following last dose of study drug(s). AEs will be tracked and followed until resolution, subject withdraws consent, or is lost to follow-up (including subjects who discontinue early). All adverse events collected per the protocol will be followed with appropriate medical management until they are resolved, if they are related to the study treatment, or until the investigator deems the event to be chronic.

Please see Table 7 to identify the adverse events that need to be reported.

7.2.2 Reporting of Adverse Events and Serious Adverse Events

All serious adverse events (SAEs) that occur after the subject has signed the consent form through 30 days following last dose of study drug(s) will be reported. All SAEs will be followed until satisfactory resolution, or until the investigator deems the event to be chronic.

All serious adverse events (SAEs) must also be documented in OnCore®.

7.2.2.1 Reporting Instructions — Serious Adverse Events — Reported within 24 Hours

Serious adverse events requiring reporting within 24 hours (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) chair via an email to saenotify@uwcarbone.wisc.edu within one business day. The OnCore® SAE Details Report must be submitted along with other report materials as appropriate (NCI AERs form or FDA Medwatch Form no. 3500 and/or any other documentation available at that time of initial reporting). The DSMC chair will review the information and determine if immediate action is required.

Within 10 working days, all available subsequent SAE documentation must be submitted electronically along with a 24-hour follow-up SAE Details Report and a completed UWCCC SAE Routing Form to saenotify@uwcarbone.wisc.edu. All information is entered and tracked in the UWCCC database.

The principal investigator notifies all investigators involved with the study at the UWCCC, the IRB, the sponsor, and the funding agency and provides documentation of these notifications to the DSMC. If the SAE occurs on a clinical trial in which the UW PI serves as the sponsor investigator, the PI reviews the event to determine whether the SAE requires reporting to the FDA and other participating investigators. For a multiple institutional clinical trial, the PI is responsible for ensuring that SAEs are reported to the sponsor as well as to all participating investigators. See Section 7.3 for detailed instructions on SAE reporting**.**

7.2.3 Serious Adverse Events — Reported within 10 Days

Serious adverse events requiring reporting within 10 days (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) chair via an email to saenotify@uwcarbone.wisc.edu. The OnCore® SAE Details Report must be submitted along with other report materials as appropriate (NCI AERs form or FDA Medwatch Form no. 3500 and/or any other documentation available at the time of initial reporting). The DSMC chair will review the information and determine if further action is required. All information is entered and tracked in the UWCCC database.

The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB, the sponsor, and the funding agency and provides documentation of these notifications to the DSMC.

If the SAE occurs on a clinical trial in which the UW PI serves as the sponsor-investigator, the PI reviews the event to determine whether the SAE requires reporting to the FDA and other participating investigators.

For a multiple institutional clinical trial, the PI is responsible for ensuring SAEs are reported to the sponsor as well as to all participating investigators.

7.2.4 Sponsor-Investigator Responsibilities for SAE Review

In the event the UWCCC principal investigator is acting as the sponsor-investigator (i.e., the PI holds the IND), the PI assumes responsibilities of the study sponsor in accordance with FDA 21 CFR 312.32. In this capacity, the UWCCC PI reviews all reports of serious adverse events occurring on the study at UWCCC and participating external sites and makes a determination of 1**) suspectedness** (i.e., whether there is a reasonable possibility that the drug caused the AE); and 2) **unexpectedness** (the event is not listed in the investigator's brochure or is not listed at the specificity or severity that has been observed) in the context of this study. SAEs with suspected causality to study drug and deemed unexpected are reported as IND Safety Reports by the UWCCC PI to the FDA, all participating investigators on the study, and the external global sponsor (if applicable) within 15 calendar days. All fatal or life-threatening SAEs that are unexpected and have suspected causality to the study drug will be reported by the UWCCC PI to the FDA, all participating investigators on the study, and the external global sponsor (if applicable) within seven calendar days.

7.2.5 Study Progress Review

Protocol summary reports (PSR) are required to be submitted to the DSMC in the time frame determined by the risk level of the study (when known or per the WON guidelines (i.e., semi-annually)). The PSR provides a cumulative report of SAEs, as well as instances of noncompliance, protocol deviations, and unanticipated problems, toxicities and responses that have occurred on the protocol in the time frame specified. PSRs for those protocols scheduled for review are reviewed at each DSMC meeting.

Protocol summary reports enable DSMC committee members to assess whether significant benefits or risks are occurring that would warrant study suspension or closure. This information is evaluated by the DSMC in conjunction with other reports of quality assurance activities (e.g., reports from internal audits, quality assurance reviews) occurring since the prior review of the protocol by the DSMC. Additionally, the DSMC requires the study team to submit external DSMB or DSMC reports, external monitoring findings for industry-sponsored studies, and any other pertinent study-related information.

In the event that there is significant risk warranting study suspension or closure, the DSMC will notify the PI of the DSMC findings and ensure the appropriate action is taken for the protocol (e.g., suspension or closure). The DSMC ensures that the PI reports any temporary or permanent suspension of a clinical trial to the sponsor (e.g., NCI program director, industry sponsor medical monitor, cooperative group study chair) and other appropriate agencies. DSMC findings and requirements for follow-up action are submitted to the CRC.

7.3 Expedited Reporting of Serious Adverse Events

Depending on the nature, severity, and attribution of the serious adverse event, an SAE report will be phoned in, submitted in writing, or both according to the table below. All serious adverse events must also be reported to the UWCCC Data and Safety Monitoring Committee Chair. All serious adverse events must also be reported to the UW IRB (if applicable), and any sponsor/funding agency not already included in the list.

Determine the reporting timeline for the SAE in question by using the following table. Then refer to sections 7.3.3 AMD 7.3.5 below if the SAE occurred at the UWCCC or sections 7.3.4 and 7.3.5 if the SAE occurred at 1 South Park, Johnson Creek, or a WON Site.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1,2]

TABLE 7:- FDA Reporting Requirements for Serious Adverse Events (21 CRF Part 312)

NOTE: Investigators **MUST** immediately report to the UWCCC and any other parties outlined in the protocol ANY serious adverse events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

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

1) Death.
2) A life-threatening adverse event.
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IMEs) 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 (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the UWCCC within the time frames detailed in the table below:

Hospitalization	Grade 1 and Grade 2 Time Frames	Grade 3-5 Time Frames
Resulting in hospitalization ≥ 24 hrs	10 Calendar Days	24 Hour; 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- **24-Hour; Five Calendar Days** – The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within five calendar days of the initial 24-hour report.
- **10 Calendar Days** – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within five calendar days for:

- All grade 3, 4, and 5 AEs.

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization.

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

7.3.1 SAE Requiring [24] Hour Reporting Occurs at UWCCC

Report to the UWCCC:

Reference the **SAE SOP** (Standard Operating Procedure) and the **SAE Reporting Workflow for DOTs** on the UWCCC website (https://kb.wisc.edu/uwccc/internal/41020) for specific instructions on how and what to report to the UWCCC for [24] hour initial and follow-up reports. **A follow-up report is required to be submitted within 10 days of the initial [24] hour report.**

For this protocol, the following UWCCC entities are required to be notified:

a) saenotify@uwcarbone.wisc.edu
b) Sailaja Kamaraju, MD, MS: skamaraju@mcw.edu
c) Kari Wisinski, MD: kbwisinski@medicine.wisc.edu
d) Tamara Koehn: tmkoehn@medicine.wisc.edu
e) Any other appropriate parties listed on the SAE Routing Form

Report to the IRB:

Consult the UW Health Sciences IRB's website for reporting guidelines.

7.3.2 SAE Reporting [10] Day Reporting Occurs at UWCCC:

Report to the UWCCC:

Reference the **SAE SOP** (Standard Operating Procedure) and the **SAE Reporting Workflow for DOTs** on the UWCCC website (https://kb.wisc.edu/uwccc/internal/41020) for specific instructions on how and what to report to the UWCCC for [10] day reports.

For this protocol, the following UWCCC entities are required to be notified:

a) saenotify@uwcarbone.wisc.edu
b) Sailaja Kamaraju, MD, MS: skamaraju@mcw.edu
c) Kari Wisinski, MD: kbwisinski@medicine.wisc.edu
d) Tamara Koehn: tmkoehn@medicine.wisc.edu
e) Any other appropriate parties listed on the SAE Routing Form

Report to the IRB:

Consult the UW Health Sciences IRBs website for reporting guidelines.

7.3.3 SAE Requiring [24] Hour Reporting Occurs at a WON Site:

Report to the UWCCC:

Reference the **SAE SOP** and the **SAE Reporting Workflow for other Affiliates** on the UWCCC website (https://kb.wisc.edu/uwccc/internal/41020) for specific instructions on how and what to report to the UWCCC for [24] hour initial and follow-up reports. **A follow-up report is required to be submitted within 10 days of the initial [24] hour report.**

Send the OnCore® SAE details report and any supporting, applicable documentation to: saenotify@uwcarbone.wisc.edu

NOTE: After a WON site has submitted the [24] hour SAE follow-up report, the report is triaged initially to the UW principal investigator or study chair, the DOT program manager, the affiliate coordinator, and the DSMC chair for review.

The principal investigator or study chair is then responsible for ensuring the SAE is reported to the FDA, the global sponsor (if applicable), the UW IRB, and any other entity requiring notification, in accordance each entity's reporting requirements.

Report to the IRB:

WON sites should follow the reporting requirements of their IRB of record for SAE submission. The UW PI/study chair is responsible for the submission of the SAE to the UW Health Sciences IRBs for any sites for which the UW serves as the IRB of record.

7.3.4 SAE Requiring [10] Day Reporting Occurs at a WON site:

Report to the UWCCC:

Reference the **SAE SOP** and the **SAE Reporting Workflow for other Affiliates** on the UWCCC website (https://kb.wisc.edu/uwccc/internal/41020) for specific instructions on how and what to report to the UWCCC for [10] day reports.

Send the OnCore® SAE details report and any supporting, applicable documentation to: saenotify@uwcarbone.wisc.edu

NOTE: After a WON site has submitted the [24] hour SAE follow-up report, the report is triaged initially to the UW principal investigator or study chair, the DOT program manager, the affiliate coordinator, and the DSMC chair for review.

The principal investigator or study chair is then responsible for ensuring the SAE is reported to the FDA, the global sponsor (if applicable), the UW IRB, and any other entity requiring notification, and in accordance each entities' reporting requirements.

Report to the IRB:

The UW PI/study chair is responsible for the submission of the SAE to the UW Health Sciences IRBs. WON sites should follow their local IRB reporting guidelines for SAE submission.

7.3.5 Other Reporting Requirements

Reporting to the FDA

Serious adverse events occurring on studies on which a UW PI is acting as sponsor/investigator must be reported to the FDA within the appropriate time frame. Mandatory and voluntary reporting guidelines and instructions are outlined on the FDA website:

http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

7.4 Subject Complaints

If a complaint is received by anyone on the study staff, it will be discussed with the study staff and will be addressed on a case-by-case basis. The PI will be notified of any complaints. Complaints will be reported to the IRB if indicated.

If the subject has questions about his or her rights as a study subject, wants to report any problems or complaints, obtain information about the study or offer input, the subject can contact the research subject advocate/patient relations contact at the enrolling institution. The contact information will be provided to subjects in the consent form.

A product complaint is a verbal, written or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact the drug manufacturer and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a drug manufacturer representative. Product complaints in and of themselves are not reportable events. If a product complaint results in an SAE, an SAE form should be completed.

7.5 Risk and Benefits

7.5.1 Fulvestrant Identified Safety Risk

The most common adverse reactions observed in patients receiving fulvestrant are: injection site pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, pain in extremities, hot flashes, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea and constipation (fulvestrant U.S. prescribing information). Increased hepatic enzymes (ALT, AST, ALP) occurred in >15% of patients.

7.5.1.1 Risk of Bleeding

Because fulvestrant is administered intramuscularly, it should be used with caution in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use.

7.5.1.2 Increased Exposure in Patients with Hepatic Impairment

Fulvestrant exposure was increased in patients with moderate hepatic impairment, therefore, a dose of 250 mg is recommended in this group of patients. Fulvestrant was not evaluated in patients with severe hepatic impairment, dose modifications are allowed as mentioned in the section 6.2.

7.5.1.3 Injection Site Reaction

Injection site-related events, including sciatica, neuralgia, neuropathic pain, and peripheral neuropathy, have been reported with fulvestrant injection. Caution should be taken while administering fulvestrant per the institutional standards.

7.5.1.4 Embryo-Fetal Toxicity

Fulvestrant can cause fetal harm when administered to pregnant women. Women who are not post-menopausal or surgically sterile must be treated with a GnRH agonist to be eligible to participate. Women must not donate eggs or become pregnant during participation or for 6 months

after stopping the drugs. Male breast cancer patients participating in the trial must not donate sperm or get their partners pregnant during treatment or within 6 months after their last dose. Subjects who have sexual intercourse which may result in pregnancy will be required to use contraception during study participation and for 6 months after their last dose.

7.5.1.5 Laboratory Requirements for Postmenopausal Status

Due to structural similarity of fulvestrant and estradiol, fulvestrant can interfere with estradiol measurement by immunoassay, resulting in falsely elevated estradiol levels. Therefore, for premenopausal women, the treating providers will determine the menopausal status by either repeating the laboratory tests such as estradiol, FSH, and LH as clinically indicated, and correlate with clinical parameters.

7.5.2 Onapristone Identified Safety Risk

In the phase I trial [Cottu 2018], seven patients (13%) experienced transient dose interruptions for AEs (one each: nausea, ALT increase, gastroenteritis, GGT increased, thoracic pain, postprocedural cellulitis, LDH increase, abdominal pain and atrial fibrillation).

Thirty patients (58%) experienced at least one grade 3 or grade 4 adverse event. In 10 patients (19%), the following adverse events were considered related to ONA: increased GGT (13%), increased AST and ALP (6% each), increased bilirubin (4%), and increased ALT and LFTs, asthenia and pulmonary embolism (2% each). All except two of these AEs were associated with progressive disease: one G3 GGT elevation at week 12 in a responding patient, lasting one month with associated transient G1 AST and bilirubin increase, with no clinical symptoms; and the other a G3 GGT elevation at week 3, lasting three weeks, in a patient with liver metastases and baseline G1 GGT elevation. Both elevations decreased spontaneously with no action taken. None of the G3 AST, ALT or bilirubin elevations were considered to be dose limiting by the independent data review committee due to the presence of concurrent progressive disease in the liver.

7.5.3 ^{18}F-FFNP PET/CT Identified Safety Risk

To date, no significant adverse events have been reported as a result of the intravenous administration of ^{18}F-FFNP for PET imaging applications [54].

As with any IV administered agent, ^{18}F-FFNP could cause an allergic reaction that could potentially pose a threat to life (anaphylaxis). This has not been observed in reported human exposure to date. Reasonable precautions should be taken, consistent with normal radiologic and clinical facility practice. The patient should be monitored until the PET procedure is completed, and trained personnel and emergency equipment should be available per facility standards.

For purposes of informed consent regarding reasonably foreseeable risks to subjects in trials utilizing ^{18}F-FFNP, the following potential adverse events are considered:

- Injection-related risks that may include infection, or accidental extravasation of the dose that may lead to discomfort, localized pain, or infection (rare occurrence).
- Risks related to allergic reaction/anaphylaxis that may be life-threatening (extremely rare occurrence).

As with all PET imaging agents, ^{18}F-FFNP is a radiopharmaceutical that decays with positron emission. As such, it poses an intrinsic radiation exposure risk. The radiation effective dose equivalent to the whole body from intravenously injected ^{18}F-FFNP is estimated to be 0.02

mSv/MBq (54). Thus, for an administered dose of 7 mCi (259 MBq), the whole-body effective dose equivalent is approximately 5 mSv. The dose-limiting organ is the gall bladder, with an average absorbed dose of 0.113 mGy/MBq. The average absorbed dose to the breasts is 0.010 mGy/MBq and the whole-body dose is 0.015 mGy/MBq. The organ and total body doses associated with ^{18}F-FFNP PET imaging are comparable to or lower than those associated with other widely used clinical nuclear medicine procedures and are well below the maximum suggested individual study and annual total body dose of 30 and 50 mGy, respectively, suggested for investigational radiopharmaceuticals by the FDA.

The CT component of the PET/CT scan are used for both attenuation correction of the PET signal and for anatomic localization and not as a diagnostic CT exam. The estimated effective dose equivalent for the CT component is 5 mSv. Thus, for one ^{18}F-FFNP PET/CT scan, the whole-body effective dose equivalent is approximately 10 mSv.

7.5.4 Potential for Overlapping Toxicities

Based on the fulvestrant prescribing information and current compound- and class-related risks identified for onapristone, the following overlapping toxicities might occur:

- Nausea, vomiting, diarrhea
- Fatigue/asthenia.

For further details on clinical safety, please refer to the latest version of [Onapristone Investigator's Brochure] and the U.S. prescribing information for fulvestrant.
Since there have been no significant adverse events reported as a result of the intravenous (IV) administration of ^{18}F-FFNP for PET imaging applications, the potential for overlapping toxicities between ^{18}F-FFNP and the study treatment is considered minimal.

7.5.5 Potential for Onapristone-Fulvestrant Interactions

The potential for a drug-drug interaction between fulvestrant and coadministered drugs is considered low. There are no known drug interactions with fulvestrant. *In vitro* studies showed no relevant inhibition of the major CYP enzymes, including CYP1A2, 2C9, 2C19, 2D6 or 3A4 by fulvestrant. The lack of inhibition of CYP3A4 was confirmed in an *in vivo* interaction study with midazolam. In addition, interaction studies with rifampicin (strong CYP3A4 inducer) and ketoconazole (strong CYP3A4 inhibitor) demonstrated no effect on fulvestrant pharmacokinetics. Therefore, a DDI involving fulvestrant and onapristone are unlikely to occur [Faslodex® Prescribing Information].

8 PHARMACEUTICAL INFORMATION

8.1 Onapristone

8.1.1 Description

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 can crystallize into different polymorphic/solvated forms. During polymorph screening studies, five crystalline forms of onapristone were identified (Forms A, B, C, D and E). The chemical name of onapristone is 11β-(4-dimethylaminophenyl)-17α-hydroxy-17β-(A3-hydroxypropyl)-13α-methylgona-4, 9-dien-3-one; [also known as ZK-299; ZK-98299].

Full details are available in the investigator's brochure.

8.1.2 Aqueous Solubility

The solubility of onapristone has been determined across the physiological pH range. Onapristone is slightly too 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.

8.1.3 Packaging and Labeling

A 50 mg dose will consist of one 10 mg and two 20 mg onapristone XR tablets. The tablet strengths are differentiated by size and weight of round uncoated tablets (200 and 400 mg tablet weights). 60 tablets are packaged in a labeled HDPE bottle with child-resistant cap.

8.1.4 Storage Conditions

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

8.1.5 Stability Data

The drug substance and XR tablets are being tested for stability per the International Conference on Harmonization (ICH) guidelines.

8.1.6 Handling and Drug Accountability

The investigator is fully responsible for the investigational products at the trial site per institutional guidelines. Dispensing of investigational products will be delegated to site staff. The person responsible for dispensing the investigational products will be responsible for maintaining adequate control of the investigational products and for documenting all transaction with them.

The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of all agents. Each participating site investigator, or authorized designee, is responsible for maintaining careful record of inventory and disposition of all investigational agents received at the site. Use of the NCI Drug Accountability Record Form is recommended, but sites may use their own accountability logs per institutional standards. Sites must ensure accountability records capture the same information as the NCI Drug Accountability Record Form and in addition, capture the preparation time. Any used or partially used vials may be destroyed on site per the institutional standard of practice. Expired vials remaining at the end of the study may be destroyed onsite per institutional standards.

8.2 Fulvestrant

8.2.1 Description

Fulvestrant is an estrogen receptor antagonist indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy, HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy, HR-positive, HER2-negative advanced or metastatic breast cancer in postmenopausal women in combination with ribociclib, as initial endocrine-based therapy or following disease progression on endocrine therapy and HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy.

Full details of dose modifications are available in the package insert.

8.2.2 Aqueous Solubility

As per package insert.

8.2.3 Packaging and Labeling

Fulvestrant is commercially available.

8.2.4 Storage Conditions

As per package insert.

8.2.5 Stability Data

As per package insert.

8.2.6 Handling and Drug Accountability

As per institutional guidelines.

8.3 ^{18}F-FFNP

8.3.1 ^{18}F-FFNP Description

The chemical name of ^{18}F-FFNP is 21-[^{18}F] fluoro-16α,17α–[(R)-1'-α-furylmethylidene) dioxyl]-19-norpregn-4-ene-3,20-dione. ^{18}F-FFNP is a radiolabeled progestin analog that binds to progesterone receptor with high affinity and selectivity (7-9). In primary and metastatic breast cancer, uptake of ^{18}F-FFNP measured by PET/CT imaging has been shown to correlate with PR expression in biopsy material assayed by immunohistochemistry. ^{18}F-FFNP is primarily cleared from the body via hepatobiliary elimination.(50-54)

8.3.2 Packaging and Labeling

^{18}F-FFNP is not currently commercially available. cGMP-grade ^{18}F-FFNP will be manufactured on site in the UW-Madison Radiopharmaceutical Production Facility. This facility has been qualified and approved for production by the NCI Cancer Imaging Program and ECOG-ACRIN for clinical trials using other investigational radiopharmaceuticals, such as ^{18}F-fluoroestradiol and ^{18}F-fluorothymidine. Specific manufacturing processes will follow our approved Drug Master File for ^{18}F-FFNP. The investigational pharmacist or qualified nuclear medicine technologist will be the responsible party designated by the investigator.

^{18}F-FFNP is synthesized with high specific activity so the quantity of progestogenic material injected with the radiopharmaceutical is < 7 µg (<16.3 nmol). The final ^{18}F-FFNP product solution contains 90% (v: v) USP 0.9% sodium chloride injection and 10% (v:v) USP ethanol alcohol injection. Up to 10 mL of ^{18}F-FFNP may be administered for a single PET scan.

The injected dose of ^{18}F-FFNP will be approximately 7 mCi (259 MBq) with a specific activity greater than 200 Ci/mmol.

^{18}F-FFNP is the only active ingredient. There is no evidence that nonradioactive and radioactive FFNP molecules display different biochemical behavior.

8.3.3 Storage Conditions

In accordance with regulations, the radiopharmaceutical facility conducts several quality control tests on the ^{18}F-FFNP product prior to release for human administration. Once delivered, doses will be stored in the appropriate storage area in the nuclear medicine facility until they are administered to the subject.

The drug solution is stored at room temperature in a gray butyl septum sealed, sterile, pyrogen-free glass vial.

8.3.4 Stability Data

The expiration time of ^{18}F-FFNP is six hours.

8.3.5 Handling and Drug Accountability

The investigator is fully responsible for the investigational products at the trial site. Dispensing of investigational products will be delegated to site staff. The investigational pharmacist or qualified nuclear medicine technologist will be the responsible party designated by the investigator. The person responsible for dispensing the investigational products will be responsible for maintaining adequate control of the investigational products and for documenting all transaction with them.

9 STATISTICAL CONSIDERATIONS

9.1 Study Design

This is a single-arm phase II clinical trial to determine the efficacy and monitoring the safety of treatment with fulvestrant plus onapristone with ER-positive, (PgR-positive or PgR negative), HER2-negative locally advanced or metastatic breast cancer, which progressed on or after treatment with an endocrine therapy and a CDK4/6 inhibitor.

Tumor response to treatment will be based on RECIST 1.1 criteria using local radiological assessments. Subjects will be treated until disease progression, unacceptable toxicity, or discontinuation from the study treatment for any other reason. A total of 39 patients will be enrolled.

9.2 Sample Size

The sample size calculation for the fulvestrant and onapristone combination arm are made using Simon Two-Stage design (Simon 1989). Using a 5% non-inferiority margin, the ORR rate of 7% or lower will be considered unacceptable as the third-line treatment. The following Simon's design controls type 1 error at 5% (recommending the combination for phase III if the true ORR = 7%) and type 2 error at 20% (NOT recommending the combination for phase III if the true ORR = 20%).

A total of 39 patients will be enrolled, and the study will be conducted in two stages.

Stage I – 21 Subjects

If ≤1 response was observed, then the combination of fulvestrant and onapristone will be not considered an active treatment in this group of patients, and the trial will be terminated.

If ≥2 responses were observed, then 18 additional subjects will be enrolled.

Stage II – 18 Additional Subjects

If ≤5 of 39 responses were observed, then the combination of fulvestrant and onapristone will be not considered an active treatment in this group of subjects, and the study will be terminated.

If ≥6 of 39 responses were observed, then the activity of fulvestrant and onapristone will be considered sufficient to launch a phase III clinical trial.

This design yields a one-sided type I error rate of 5% if the ORR is 7%, and power of 80% when the true response rate of the combination is 20%.

Safety monitoring: To prevent exposing more than one-third of enrolled subjects to high levels of adverse events or severe adverse events leading to discontinuation of the combination, the following sequential procedure will be used. If the number of such discontinuation events is higher than three of the first 11 subjects, 4/21, 5/30, and 7/39 [sequential stopping boundaries for (1) 33% rate of discontinuation at a <5% chance of not stopping the study early and (2) 10% rate of discontinuation at a <10% chance of stopping the study early], the principal investigator and study chair will meet to discuss early termination of the study.

Point and 95% interval estimate of ORR will be evaluated accounting for possibility of early futility stopping as describe in Koyama T et al. 2008.(55)

PSF will be described with Kaplan-Meier (KM) Curve and its pointwise asymptotic 95% confidence bounds. Median PFS if reached will be extracted from this KM estimator. Parametric forms (such Weibull) of survival probability will be fitted to the collected data.

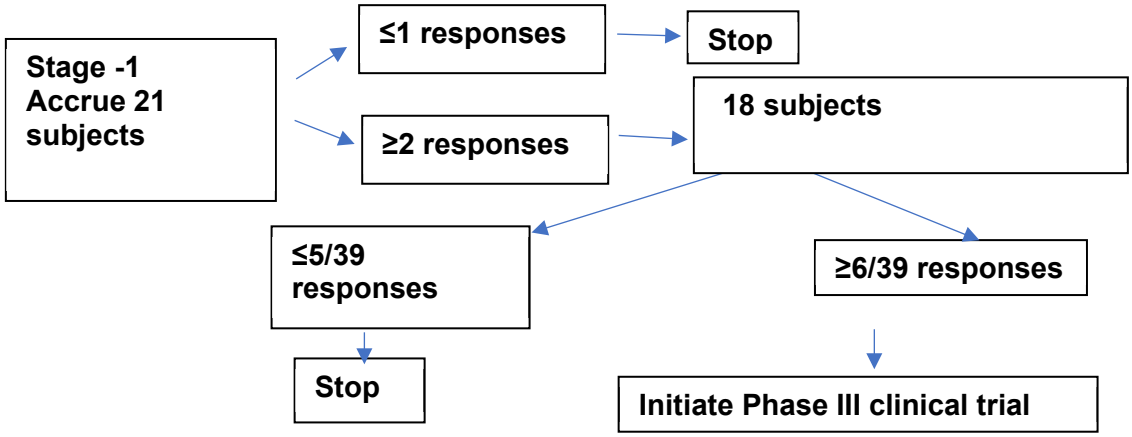
DCR will be estimated with relative frequency and exact two-sided 95% binomial confidence interval. Time from registration to first documented response (CR or PR) will be evaluated with a cumulative incidence where death will be as a competing risk to response.

Duration of response will be assessed for a subgroup of subjects with observed response. The date of response will be denoted as time zero and time to progression or death will be evaluated with KM curve and 95% CI. Median time to response will be extracted from this KM curve.

The impact of possibility of early stopping due to futility will be evaluated under plausible parametric models using Monte-Carlo simulations with 10,000 repetitions under each plausible scenario.

Type, frequency and severity of adverse events will be summarized with descriptive frequency tables.

Figure 7 Minimax Simon Two-Stage Design Enrolling 39 Subjects



Secondary analyses: Regression analysis will be completed using Cox proportional regression model for PFS and logistic regression model for ORR. Due to a relatively small number of patients in the study, we will investigate the impact of categorical variable if the number of events (responses for ORR and progression or death for PFS) is greater than five per category. The impact of the following predictors will be explored: age, race, ER status, PgR status, prior therapy (type of therapy AI or SERMs such as tamoxifen alone or CDK4/6+endocrine therapy combo), number of metastatic sites, measurable disease, and biomarkers. Single-predictor models will be used. The possibility of multiple Cox and logistic regressions will be considered as well, but due to a small number of patients we are not expecting to fit multiple regressions.

All planned data analyses will be completed with SAS 9.4. Monte-Carlo simulation studies will be completed in R v3.5.1.

10 MEASUREMENT OF EFFECT

10.1 Baseline

Imaging assessments will be performed at screening/baseline within 30 days prior to enrollment. Any imaging assessments already completed during the regular workup of the patient within 30 days prior to enrollment, including before signing the main study ICF, may be considered as the baseline images for this study.

The following assessments are required at screening/baseline:

- Chest, abdomen and pelvis CT or magnetic resonance imaging (MRI).
- CT or MRI of other metastatic sites, if clinically indicated. PET scan is an acceptable modality of imaging, as decided by the treating provider.
- Whole-body bone scan per institutional standard of care. Localized bone CT, MRI or X-ray should be performed for any lesions identified on the whole-body bone scan that are not visible on the chest, abdomen and pelvis CT or MRI.
- Brain CT or MRI, if clinically indicated.
- If skin lesions are present at screening, and amenable to photography, color photography should be acquired using a digital camera in clear focus, including a scale/ruler, in such a way that the size of the lesion(s) can be determined from the photograph.
- Measurements of breast mass on imaging are permitted as measurable disease.
- Routine blood tests prior to and during the study are listed in Table 8.

Any potentially measurable lesion that has been previously treated with radiotherapy should be considered as a non-measurable lesion, unless the lesion has clearly progressed since the radiotherapy. Chest X-rays and ultrasound should not be used to measure tumor lesions.

10.2 Response Evaluation

Imaging assessments for response evaluation will be performed every eight weeks (±7 days) during the first 12 months and every 12 weeks (±14 days) thereafter. Additional imaging assessments may be performed at any time as clinically indicated. This schedule should be followed until radiological progression is documented, irrespective of compliance to treatment, or until the subject enters follow-up.

Each lesion that is measured at baseline must be measured by the same method and the same local radiologist throughout the study.

10.3 Safety and Tolerability Assessment

Safety assessment will include routine safety monitoring of adverse events and serious adverse events; laboratory testing measurement of vital signs, performance status, physical examination and ECG will be performed at baseline and at each visit thereafter. Laboratory assessments will be performed in the local laboratory.

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 will be used for all grading. The following safety assessments will be performed along the study:

- Lab parameters: Hematology, biochemistry, coagulation, urinalysis, thyroid
- Adverse events.
- Concomitant medications.
- ECG.
- Medical history, vital signs, performance status, and physical exam.

Table 8 Clinical laboratory parameters collection plan

Test	Items
Hematology	Hematocrit, hemoglobin, MCH, MCHC, MCV, platelets, red blood cells, white blood cells, RBC morphology, differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	Calcium, potassium, sodium, glucose, alkaline phosphatase, ALT (SGPT), AST (SGOT), total bilirubin, total protein, albumin, creatinine, chloride, bicarbonate. Direct bilirubin must be performed ONLY if total bilirubin is elevated.
Coagulation at baseline	International normalized ratio (INR), and activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT).
Urine or serum pregnancy test	At baseline.

All laboratory analysis will be performed locally.

10.4 Other Assessments

Cardiac Assessments

A standard 12-lead ECG will be performed at screening. The interpretation of the ECG must be made by a qualified physician and documented in the ECG section of the CRF. Clinically significant abnormalities present when the patient signed informed consent should be reported on the medical history CRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the adverse events CRF page. Additional cardiac imaging during treatment is to be performed as clinically indicated.

10.5 Tumor Biopsy and Plasma Analyses

A summary of biomarker assessments and biomarker sample collection plan is in Tables 9, 10 and 11. All assessments will be performed by a central designated laboratory.

There are no plans to share the results with subjects. The correlative studies are not expected to provide adequate information to guide any future treatment decisions.

All FFPE tumor blocks, unstained histological slides, and research blood samples need to be shipped to:

Attn: Mary Rau
Dr. Hallgeir Rui's lab
9200 W. Wisconsin Ave.
Wisconsin Diagnostic Laboratories Building
Room L50 MCW Tissue Bank
Milwaukee, WI 53226

Sample Processing: Upon receipt of the samples, MCW's lab manager, Mary Rau, will be in charge of tissue sample processing, distribution, and shipment of the samples for

biomarker analysis by Dr. Hallgeir Rui (MCW) and Natera Inc. (**Mary Rau,** Tissue Bank Manager, Medical College of Wisconsin, Department of Pathology, mrau@mcw.edu, Office Phone: 414-805-9569, Lab Phone: 414-805-8829, Fax: 414-805-8825, MCW Tissue Bank Website: www.mcw.edu/tissuebank)

If adequate tissue is not available for all the evaluations of study biomarkers, additional biopsies may be requested. However, if a subject chooses to decline additional biopsies, he or she would still be eligible for study enrollment. Any remaining tissue of the tumor samples will be preserved as coded specimens in the MCW Tissue Bank provided the subject has provided consent for the tissue banking. Subjects who decline to participate in tissue banking will remain eligible for the proposed study. FFPE blocks are stored long-term in metal Sakura block cabinets under ambient temperature. Room temperature is recorded and monitored daily. Samples are logged and tracked in the MCW Tissue Bank's tissue tracking software, OnCore®.

10.5.1 Tissue Analysis

An FFPE tumor biopsy block or up to 20 superplus frost slides, with unstained histological sections at 5 micrometer thickness are required at the time of study entry. A single H&E slide is also requested.

If the archival tissue has not been obtained in the 18 months prior to study registration, analysis of a more recent biopsy will be required for study entry if deemed safe (minimal risk to patient) by the treating physician. ER/PR/HER2 testing will be performed at the facilities/clinics where the patients are routinely seen, and the biopsy was performed. The remaining block will be sent (for sectioning or 20 precut sections) to Mary Rau at the above-mentioned address.

1. **Tissue analysis for IHC, protein expression and other makers (performed by Dr. Hallgeir Rui, MD, PhD):** Protein expression will be quantified on slides, using optimized immunohistochemistry [IHC] protocols for planned study biomarkers. Ki-67 assessment on pre- and post-treatment specimens would include assessment by manual counting of stained tumor cells by our pathologists, as well as quantitative IHC.

2. The degree of PgR expression levels will be determined using standard immunohistochemistry methodology on all tissue and reported as percent tumor cells with PgR staining. In cases where no PgR results are available, one to three 4-micrometer histological sections on superplus frost slides will be used for IHC testing. This testing will be performed at the Medical College of Wisconsin 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 PgR expression, and/or PgR signaling, will be examined.

3. Additional exploratory biomarkers will be evaluated on FFPE tissue, including phosphorylated PgR and PgR target gene expression. If ≥ 1% phosphorylated Ser294 PgR (pPgR) tumor staining is seen on ≥ 1 slide the tumor will be considered to be pPgR+. Nuclear localization of pPgR will also be evaluated. PgR target gene analysis will be completed using the NanoString nCounter oncology panel system. NanoString analysis will require 25 ng of FFPE tissue. Tables 9, 10 and 11 include a complete list of tissue and blood-based genomic alterations of the breast tumor samples, and their preparation for this study.

4. **Tissue analysis for ctDNA testing (performed by Natera)**: Tumor samples will be

processed and shipped to Natera for ctDNA testing as noted above.

Table 9		
Biomarker Correlatives	**Tissue Biopsy**	**Liquid Biopsy (Plasma)**
Collection	Pre-treatment core biopsy (archival or new FFPE biopsy) and post-treatment core biopsy (FFPE; if available)	Three time points: pre, during (C3D1) and post-treatment (or at next follow-up visit)
Immunohistochemistry (IHC)	ER, PgR, HER2, Ki67, CD24, CD44, LDH1, KLF4, CK 5/6, Phospho-Ser294-PgR	
Mutational Analysis of the tumor tissue (performed by Natera)	A personalized assay is designed based on the unique mutation signature of each patient's tumor	A personalized assay is designed based on the unique mutation signature of each patient's tumor and correlated with peripheral blood. This will allow to accurately monitor for the presence or absence of the disease over time.

10.5.2 Peripheral Blood Preparation, Storage, and Preservation

The proposed study aims to evaluate genomic alterations and or others (from a routine blood draw) for research purposes to be performed for this cohort of subjects with ER+/HER2- breast cancer. The blood samples will be prospectively collected at various time points and retrospectively evaluated (i.e., pretreatment, , Cycle 3 Day 1 and post-treatment on the study) (if post-treatment blood draw is not collected for any given reason, the treating provider may choose to do a blood sample collection at the follow-up visit).

The blood sample collection will be per Natera (Signatera ™) guidelines for possible blood marker analysis for research purposes. Peripheral blood received fresh in the MCW Tissue Bank from consented participants. Sample collection kits (provided by Natera) will be used for blood collection.

Blood samples for Germline testing: Two 10 mL Streck tubes of blood will be collected pre-treatment, at Cycle 3 Day 1 and at the end of treatment for germline testing. The tube should be inverted a couple times after collection and shipped to MCW (see operations manual for further instructions).

Matched Normal Blood – in the form of frozen buffy-coat or frozen whole blood in a purple top EDTA (>1ml frozen whole blood, >200ul buffy coat). A 6 mL EDTA tube will be collected pre-treatment. The tube should be inverted a couple times after collection and shipped to MCW (see operations manual for further instructions).

10.5.3 Functional Imaging

18F-FFNP PET/CT Imaging Protocol

For this study, PR functional imaging using ^{18}F-FFNP PET/CT will be performed for up to 12 subjects. Quantitative molecular imaging with ^{18}F-FFNP PET/CT before and seven to 14 days after starting therapy may be useful to confirm optimal dosing of onapristone to block PR binding to ^{18}F-FFNP in patients with extrahepatic metastases. Incomplete receptor blockade, indicating suboptimal dosing, may be associated with earlier disease progression. The change in tumor ^{18}F-FFNP uptake after starting therapy will be evaluated as an estimate of PR binding availability. Tumor ^{18}F-FFNP uptake parameters (SUV_{max}, SUV_{mean}, SUV_{peak}, tumor-to-normal tissue uptake ratio, functional tumor volume, and total lesion uptake) will be measured before and after starting therapy.

PET/CT scanners at UW-Madison are qualified by the American College of Radiology (ACR) Imaging Core Laboratory and have been approved for use in current ECOG/ACRIN trials. The scanner routinely will be assessed for quantitative integrity and stability by being tested using various imaging protocols on a standard phantom. For SUV measurement, this includes a comparison against a dose calibrator to ensure accuracy. A daily QC check will be performed at the beginning of the day, including PET/CT scanner and dose calibrator, in accordance with the manufacturer recommendations. If any of the QC results are outside of the manufacturer's guidelines, the study will be rescheduled, and the problem rectified before scanning any subjects. 18F-FFNP PET/CTs not completed within the protocol-specified windows due to QC results will not be considered a protocol deviation.

A PET Imaging Protocol Manual specific to this clinical trial will be prepared for the research study coordinators and nuclear medicine technologists at UW-Madison. Subjects do not need to be fasting for 18F-FFNP PET/CT imaging, but will be encouraged to be well hydrated. The subject's weight will be measured the day of imaging. 18F-FFNP will be synthesized according to cGMP requirements and processed for QA/QC by the UW Radiopharmaceutical Production Facility. For each research imaging session, subjects will receive 18F-FFNP, approximately 7 mCi (259 MBq), IV slow infusion over approximately two minutes followed by saline flush, once administered in the PET imaging suite.

After approximately 60 minutes of uptake time, the subject will be positioned supine in the PET/CT scanner (Discovery 710 or Discovery MI at UW-Madison) for a standard body PET/CT scan from skull vertex to mid-thigh (typically five to seven fields of view depending on scanner specifications and the subject's height) covering all known sites of metastatic disease and will include normal organs with expected 18F-FFNP uptake (pituitary gland and uterus). This scan will usually take approximately 20 to 30 minutes, depending upon the scanner used. Subjects will be asked to void prior to and soon after the exam to further minimize radiation dose to the urinary bladder. All sequential PET/CT imaging sessions will be performed on the same scanner to minimize variability. An iterative ordered-subsets expectation maximization algorithm will be used for PET image reconstruction. The PET data will be corrected for attenuation and scatter and co-registered with the CT images.

All adverse events occurring within a 24-hour period post-18F-FFNP infusion will be recorded from the subject within one to three days post-18F-FFNP infusion. Events to be specifically monitored during the infusion include localized discomfort at the IV injection site, pain, respiratory difficulties, flushing, dizziness, pruritus/rash, and any other symptoms that could be secondary to an anaphylactic reaction. The subject will be instructed to report any symptoms or sensory changes noted.

10.5.4 18F-FFNP PET/CT Imaging Analysis

18F-FFNP PET/CT images will be reviewed for general quality, including quality of the PET images, quality of CT images, the adequacy of PET/CT alignment, and the presence of any significant attenuation artifact. Lesions of interest will be visually identified by 18F-FFNP uptake and confirmed on at least one other conventional imaging modality, which may include the CT portion of the same PET/CT examination. Each site of disease will be analyzed for (1) qualitative and (2) quantitative 18F-FFNP uptake. For subjects with innumerable lesions, an arbitrary maximum of five lesions will be recorded.

10.5.5 Qualitative Analysis of 18F-FFNP Uptake (Lesion-Level)

18F-FFNP uptake will be evaluated qualitatively with the following scale: no uptake (tumor < background), minimal uptake (tumor = background), mild (tumor slightly > background), moderate uptake (tumor >> background), and intense uptake (tumor >>> background). Tumor uptake will be defined as increased (moderate or intense uptake) or absent (no uptake, minimal or mild uptake) for up to five target lesions.

10.5.6 Quantitative Analysis of 18F-FFNP Uptake (Lesion-Level)

Up to five target lesions with increased 18F-FFNP uptake, as defined by the qualitative analysis, will be further evaluated. Regions of interest (ROI) will be manually drawn to include the tumor and 18F-FFNP uptake will be quantified using standardized uptake value (SUV) measurements including SUVmax, SUVmean, SUVpeak, tumor-to-normal (T/N) tissue ratio, and tumor-to-blood pool ratios.

10.5.7 Definition of 18F-FFNP Blockade

The same five target lesions will be analyzed for quantitative 18F-FFNP uptake on the second 18F-FFNP PET/CT examination as on the initial scan. If the SUVmax for all five lesions have decreased by > 75% or all five lesions have SUVmax < 1.5 on the second scan, then these subjects will be prospectively defined as having complete 18F-FFNP blockade. If the SUVmax for any of the five lesions has not decreased by > 75% or if any new lesions arise with SUVmax ≥1.5, then these subjects will be defined as having incomplete 18F-FFNP blockade. Changes in radiotracer uptake in normal organs with expected 18F-FFNP uptake (pituitary gland and uterus) will also be measured as an internal reference.

11 DATA AND SAFETY MONITORING PLAN (DSMP)

11.1 Oversight and Monitoring Plan

The UWCCC Data and Safety Monitoring Committee (DSMC) regularly reviews and monitors clinical research at the UWCCC and WON. A summary of DSMC activities are as follows:

- Reviews clinical trials conducted at the UWCCC for subject safety, protocol compliance, and data integrity.
- Reviews serious adverse events (SAEs) requiring expedited reporting, as defined in the protocol, for clinical trials conducted at the UWCCC, and studies conducted at external sites for which the UWCCC DSMC acts as an oversight body.
- Reviews reports generated through the UWCCC Data and Safety Monitoring System (DSMS) elements (e.g., internal audits, quality assurance reviews, compliance reviews, response reviews, and protocol summary reports).
- Notifies the UWCCC protocol principal investigator of DSMC decisions, recommendations, and, if applicable, any requirements for corrective and/or preventive actions related to data or safety issues.
- Works in conjunction with the UW Health Sciences IRB in the review of relevant safety information, as well as non-compliance and unanticipated problems reported to the IRB.
- Ensures that notification of SAEs requiring expedited reporting is provided to external sites participating in multi-site clinical trials coordinated by WON.

11.2 Monitoring and Reporting Guidelines

UWCCC quality assurance and monitoring activities are determined by study type, study sponsorship, and risk level of the protocol as determined by the UWCCC Protocol Review and Monitoring Committee (PRMC).

Protocols subject to intermediate monitoring generally include UW institutional phase I/II and phase II Trials. These protocols undergo review of subject safety at regularly scheduled DOT meetings where the results of each subject's treatment are discussed, and the discussion is documented in the DOT meeting minutes. The discussion includes the number of subjects enrolled, significant toxicities, dose adjustments, and responses observed. Protocol summary reports are submitted on a semi-annual basis by the study team for review by the DSMC.

11.3 UWCCC DSMC Study Progress Review

The review of protocol summary reports (PSRs) enables the UWCCC DSMC to assess whether the study should continue, continue with modifications, be suspended, or be closed. Following their review, the UWCCC DSMC will notify the PI of their recommendation and the authority for continuing, modifying, suspending, or closing the protocol is the responsibility of the applicable sponsor-investigator, PI, IRB, FDA, or other regulatory authority associated with the protocol.

Based on the risk level of this study, as determined by the UWCCC PRMC, PSRs must be submitted to the UWCCC DSMC by the UWCCC site study team on a twice-yearly basis.

The UWCCC Affiliate Office is responsible for coordinating with WON sites to ensure the data used to populate the PSRs are entered into the UWCCC OnCore® in a timely manner. This data includes, but are not limited to accrual information, SAEs, response to treatment, IRB reportable events (e.g., non-compliance, unanticipated problems).

11.4 UWCCC DSMC Review of Auditing and/or Monitoring Reports

Reports created through the auditing and/or monitoring activities at all participating sites are submitted in real time to the UWCCC DSMC by the UWCCC staff performing these activities. Summary data and/or query reports are submitted in lieu of detailed reports. Following the review of these reports, the UWCCC DSMC may issue a request for additional corrective and/or preventive action(s), protocol suspension, or for-cause audit(s).

11.5 UWCCC DSMC Review of Noncompliance, Unanticipated Problem, and other IRB Reportable Events

Participating sites are to follow the reporting guidelines of their IRB of record. The UWCCC Affiliate Office will assist sites with study wide event data that are required to be reported. If WON sites utilize the UW IRBs as their IRB of record, submissions are to be coordinated with the UWCCC Affiliate Office.

IRB reportable events are to be submitted to the UWCCC DSMC via an email to DSMC@uwcarbone.wisc.edu at the same time they are submitted to the IRB of record.

11.6 UWCCC DSMC Review of Serious Adverse Events

The UWCCC DSMC chair, or designee, reviews all SAEs occurring on the study in real time, regardless of site, to determine if immediate action is required.

12 REGULATORY COMPLIANCE, ETHICS AND STUDY MANAGEMENT

12.1 Ethical Standard

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

12.2 Regulatory Compliance

This study will be conducted in compliance with:

- The protocol
- Federal regulations, as applicable, including: 21 CFR 50 (Protection of Human Subjects/Informed Consent); 21 CFR 56 (Institutional Review Boards) and §312 (Investigational New Drug Application; and 45 CFR 46 Subparts A (Common Rule), B (Pregnant Women, Human Fetuses and Neonates), C (Prisoners), and D (Children), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

12.3 Prestudy Documentation

Prior to implementing this protocol, the protocol, the informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the UW Health Sciences IRB. Prior to implementing this protocol at the participating sites, approval for the UW Health Sciences IRB-approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to UWCCC before the participating site can be initiated and begin enrolling participants:

- Participating site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization.
- Participating site IRB approved consent form.
- Participating site IRB membership list.
- Participating site IRB's Federal Wide Assurance number and OHRP registration number.
- Curriculum vitae and medical license for each investigator and consenting professional.
- Documentation of Human Subject Research Certification training for investigators and key staff members at the participating site.
- Participating site laboratory certifications and normals.

Upon receipt of the required documents, UWCCC will formally contact the site and grant permission to proceed with enrollment.

12.4 Institutional Review Board

The protocol, the proposed informed consent form and all forms of participant information related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by the UW Health Sciences IRB (or designated central IRB). Prior to obtaining UWCCC approval, the protocol must be approved by the UWCCC Protocol Review and Monitoring Committee. The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

After the UW Health Sciences Institutional Review Board (HS-IRB) (or designated central IRB) grants initial approval for a WON study, the affiliate coordinator provides the WON sites with the approved documents. Sites use the IRB-approved consent document for UWCCC as a template. WON sites may make minor changes to the consent form to reflect their institutional standards. No substantial changes, including changes to the risk language, are allowed (sites can always clarify existing risk information or add risk language if they wish to do so).

Each WON site must receive local IRB approval of both the UW IRB (or designated central IRB) approved protocol and informed consent/HIPAA documents (with minor revisions allowed). The local IRB approval notice and informed consent documents are forwarded to the affiliate coordinator at the address listed below. Once all of UWCCC administrative requirements are completed and local IRB approval is verified, the affiliate coordinator issues an activation notice for the site. Study activities can begin at the local site only once this activation notice is issued.

Any site under the UW HS-IRB's (or designated central IRB) purview must receive UW HS-IRB approval for its participation prior to study activation at the site. UWCCC-Johnson Creek uses the same UW HS-IRB (or designated central IRB) approval process and consent form as UW. Of note, member sites of the Wisconsin IRB Consortium (WIC), may be approved for participation through IRB deferral agreements made possible by the WIC mechanism. Both UWCC-Johnson Creek and WIC institutions must also be issued activation notices prior to enrolling subjects.

The affiliate coordinator is responsible for continued oversight of regulatory documentation for each WON site. The affiliate coordinator distributes all additional UW HS-IRB (or designated central IRB) approved amendments and consents to participating WON sites. The affiliate coordinator uses OnCore® and additional spreadsheets to track local IRB approvals of all amendments and consents for participating WON sites. All local IRB approvals and informed consent documents should be forwarded to the affiliate coordinators at the UWCCC by email (affiliatecoordinators@uwcarbone.wisc.edu) or regular mail:

Affiliate Coordinators
University of Wisconsin Carbone Cancer Center
600 Highland Avenue, CSC, K4/6
Madison, WI 53792-6164

12.5 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product.

Potential subjects will be told, and a statement will be included that this study is designed to determine both safety and effectiveness. The consent forms will include the approved UW Health Sciences IRB template language.

Consent forms will be IRB-approved, and the subject will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. In accordance with 46 CR 46.111, the subject will sign and date the informed consent document prior to any procedures being done specifically for the study.

The subjects will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial.

A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. If there are changes to the consent form, all revisions will be reviewed with study subject at the next appropriate opportunity. Subjects that require reconsenting will be defined in the IRB-approved amendment submission. The process for obtaining informed consent will again be performed. Study subjects will not be reconsented for continuing reviews. Sites should follow their IRB's policy for subjects who demonstrate limited English proficiency or limited literacy.

After the subject's visit in which the consent is signed, it is documented in the clinic chart that the consent has been signed and that all questions have been answered to the subject's satisfaction after adequate time for review of the consent. It is also documented that a copy of the consent is given to the subject. The original consent is kept with the subject's study file, and a copy of the consent is sent for inclusion in the legal medical record.

All WON sites under the purview of their local IRBs follow recruitment and consent processes approved by the local IRB of record.

Documentation of both the informed consent process and that the process occurred prior to a subject's entry into a WON study is recorded in the subject's source documents. The original consent form, signed and dated by the subject and by the person consenting the subject, must be maintained in the investigator's study files at each site. All current FDA, NCI, state, federal and Institutional regulations concerning informed consent will be followed.

12.6 Subject Confidentiality and Access to Source Documents/Data

Subject confidentiality is strictly held in trust by the principal investigator and all research staff. This confidentiality includes the clinical information relating to participating subjects, as well as any genetic or biological testing.

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 principal investigator/study chair

The conditions for maintaining confidentiality of the subjects' records are required for the life of the data. Identifiable subject information will be maintained at the enrolling site. All source documentation will be maintained within the subject's research chart which will be accessible only to authorized study personnel. Subject research charts will be stored in a locked research office at each enrolling site.

Study data will be collected via the UWCCC Oncore® database. Each enrolling site is responsible for entering data into study specific eCRFs. Subject data used for analysis will be coded. Databases in which the study subject information is stored and accessed are password protected, allowing for limited access by authorized personnel only. Data/PHI kept in the electronic case report forms contain the study identifiers, subject initials, date of birth and date of service.

Personal identifiers, such as name and medical record number, will be removed from accompanying laboratory reports and test results. Any data/PHI that are not stored for the purposes of the study are shredded in the Clinical Trials Office.

After all study queries and analyses are completed, the data/PHI will not be destroyed but will be archived in a secure long-term storage site in order to keep an accurate record of screened and enrolled subjects for the sponsor and potential audit purposes only specific for this study. Data/PHI would not be destroyed until permission is granted by the sponsor to destroy the records.

The principal investigator/study chair will allow access to all source data and documents for the purposes of monitoring, audits, IRB review, and regulatory inspections.

The study monitors or other authorized representatives of the principal investigator/study chair may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. Each clinical study site will permit access to such records.

12.7 Protection of Human Subjects

12.7.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the informed consent process. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

12.7.2 Protection of Privacy

As noted, subjects will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be invited to sign informed consent documents. The original signed document will become part of the subject's medical records, and each subject will receive a copy of the signed documents.

12.8 Investigator Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies).

Onsite Audits

WON sites will be audited in accordance with the WON auditing and monitoring plan.

Regulatory authorities, the IRB and/or sponsor may request access to all source documents, data capture records and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

13 DATA HANDLING AND RECORD KEEPING

13.1 Overview

Every effort is made to uphold the integrity of the project, the research, the institution, and the researchers involved. Data collection guidelines and methodologies are carefully developed before the research begins. Investigators focus on the following to ensure data integrity: well-trained data collectors/recorders to ensure consistency and quality, well-designed data collection protocols and ongoing monitoring. In this way, study rigor and validity are maintained. Data are protected from physical damage as well as from tampering, loss or theft. This project's data management is a multidisciplinary activity that includes investigators, research coordinators and nurses, data mangers, support personnel, biostatisticians and database programmers. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

13.2 Data Management Responsibilities

13.2.1 Principal Investigator

The principal investigator oversees the management of subject records/case report forms and ensures that a) complete and accurate data will be obtained and provided to the sponsor; b) subject records are maintained to include history, prescribed medication and investigational product(s), measurements, exams, evaluations and adverse events; c) corrections are applied to clinical research data according to principles of good research practice (i.e., single-line delete, date and initial). He or she will ensure that there is correlation between the case report forms and the source documents**.** The principal investigator will have additional oversight responsibilities as applies to subjects enrolled through Wisconsin Oncology Network affiliate sites:

- Verify that weekly summaries are obtained and verified.
- Review all SAEs submitted by WON sites.

- Verify remote or on-site auditing occurs at participating WON sites.

13.2.2 Research Coordinator

A research coordinator creates, collects and organizes clinical trial documentation. He or she ensures that source documentation and data abstraction and entry are being done at protocol-specified time points.

13.2.3 Research Nurse/Medical Staff

The research nurse and medical staff documents protocol-required care or assessment of the subject's outcomes, adverse events and compliance to study procedures.

13.2.4 Biostatistician

The biostatistician may assist in CRF development (content and design), dataset specifications (annotation of CRFs and record layout) and validation.

13.3 Handling and Documentation of Clinical Supplies

The principal investigator will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of subjects to whom study drug has been dispensed by subject number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The principal investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the principal investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

13.4 Source Documents

Source documents for clinical information (e.g., patient history, diagnosis, clinical and diagnostic test reports) are maintained in the patient's clinical file. Source documents for the correlative studies are maintained in the laboratory conducting the study.

All source documents will be written following ALCOA standards:

Table 12 ALCOA Attribute	Definition
Attributable	Clear who has documented the data.
Legible	Readable and signatures identifiable.
Contemporaneous	Documented in the correct time frame along with the flow of events. If a clinical observation cannot be entered when made, chronology should be recorded. Acceptable amount of delay should be defined and justified.
Original	Original, if not original should be exact copy; the first record made by the appropriate person. The investigator should have the original source document.
Accurate	Accurate, consistent and real representation of facts.
Enduring	Long-lasting and durable.

Table 12 ALCOA Attribute	Definition
Available and accessible	Easily available for review by treating physicians and during audits/inspections. The documents should be retrievable in reasonable time.
Complete	Complete until that point in time.
Consistent	Demonstrate the required attributes consistently.
Credible	Based on real and reliable facts.
Corroborated	Data should be backed up by evidence.

13.5 Case Report Forms

The principal investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study-specific case report forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs, in accordance with the study calendar, using single data entry with a secure access account. The clinical research coordinator will complete the CRFs as soon as possible upon completion of the study visit; the investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the subject's medical records maintained by each site's personnel. All source documentation should be kept in separate research folders for each subject.

In accordance with federal regulations, the investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs.

All source documentation and data will be available for review/monitoring by the UWCCC DSMC and regulatory agencies.

13.6 Study Record Retention

The principal investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity and use by subjects, as well as written records of the disposition of the drug when the study ends.

The principal investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

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

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

In accordance with FDA regulations, the investigator shall retain records for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified.

13.7 Institutional Review Board (IRB) Approval

The protocol, informed consent form, HIPAA authorization and any other applicable documents must be approved by the UW HS-IRB prior to activating the protocol at UW. Once UW has IRB approval, the UWCCC Affiliate Office is responsible for disseminating the IRB-approved documents to the WON sites and collecting the required regulatory documents for activation as outlined in the Study Operations Manual.

The UW PI is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. The protocol must be reapproved by the IRB, as local regulations require.

The Affiliate Office is responsible for continued oversight of regulatory documentation for each WON site. The affiliate coordinator distributes all additional HS-IRB approved amendments to WON sites and is responsible for tracking local IRB approvals as outlined in the Study Operations Manual.

13.8 WON Site Oversight

The UWCCC Affiliate Office serves as the coordinating center for WON. Coordinating center responsibilities are shared between the affiliate coordinator and UWCCC Breast/Melanoma DOT. A detailed description of coordinating center responsibilities, as well as other WON processes and procedures, is provided in the WON Manual available on the UWCCC website.

Regular communication between the UWCCC Affiliate Office and WON sites ensures that all participating parties are notified of protocol changes, informed consent document revisions, action letters, study status changes, reportable events/serious adverse events (as necessary), and any other applicable information. This communication is accomplished through regular email updates and conference calls.

APPENDIX 1. PERFORMANCE STATUS CRITERIA

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

APPENDIX 2: SUBJECT LOST TO FOLLOW-UP LETTER

Date: _____

Dear _____,

The research study team has been unable to contact you regarding the clinical trial (A Phase II Trial of Onapristone in Combination with Fulvestrant for women with ER-positive, PR-positive and HER2-negative Metastatic Breast Cancer after Progression on Aromatase and CDK 4/6 Inhibitors) you participated in.

We would like to discuss how you are doing and if we may continue contacting you.

Please contact us at
_____

Sincerely,

_____

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