Cover Page

Title: Study Protocol with Statistical Analysis Plan

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Clinical Study Protocol

An Open-Label, Phase 1b-2 Study of Elacestrant, in Combination with Onapristone in Patients with Estrogen Receptor-Positive, Progesterone Receptor-Positive, HER2-negative Advanced or Metastatic Breast Cancer (ELONA)

Version:	1.0
Approval Date:	August 29, 2022
IND Number:	114232
Sponsor:	Context Therapeutics 2001 Market Street, Suite 3915, Unit #15 Philadelphia, PA 19103 USA

GCP Statement: This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement: The information contained in this document is the property of the Sponsor and is confidential. It contains proprietary information of Context Therapeutics (the sponsor), Menarini Ricerche SPA and Stemline Therapeutics, a member of the Menarini Ricerche group of companies. Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study. These restrictions will apply after the study has been closed.

The protocol has been approved by Context Therapeutics

Sponsor Signatory: Tarek Sahmoud, MBBCh, PhD

Signature *Tarek Sahmoud* *Electronically signed by: Tarek Sahmoud*
Reason: I approve this document
Date: Sep 2, 2022 15:27 GMT+1 Date

INVESTIGATOR PROTOCOL AGREEMENT

ONA-XR-103: An Open-Label, Phase 1b-2 Study of Elacestrant, in Combination with Onapristone in Patients with Estrogen Receptor-Positive, Progesterone Receptor-Positive, HER2-negative Advanced or Metastatic Breast Cancer (ELONA)

I hereby agree to:

- ✓ Conduct the study as outlined in this protocol with reference to national/local regulations and current International Council for Harmonisation (ICH) / Good Clinical Practice (GCP) guidelines.
- ✓ Maintain the confidentiality of all information received or developed in connection with this protocol.
- ✓ Fully co-operate with monitoring and auditing and allow access to all documentation by authorized individuals representing Stemline Therapeutics, Inc., or Health authorities.

Protocol Version: Version 1 (29Aug2022)

To be signed by Principal Investigator at the Site:

Print Name			
Signature		**Date**	
Institution			

PROCEDURES IN CASE OF EMERGENCY

Emergency contact information can be found on the subject identification card.

1 CLINICAL PROTOCOL SYNOPSIS

Compound names	Elacestrant and onapristone	
Study Title	An open-label, Phase 1b-2 study of **EL**acestrant, in combination with **ONA**pristone in patients with estrogen receptor-positive, progesterone receptor-positive, HER2-negative advanced or metastatic breast cancer (**ELONA**)	
Phase of Development	Phase 1b-2	
Study Centers	Approximately 19 sites in the United States	
Principal Investigator	Erika Hamilton, MD, Tennessee Oncology, Nashville, TN, USA	
Study duration	Approximately 3 years: • 15 months recruitment, • 6 months additional follow-up for primary analysis, • 18 additional months for updated analysis and overall survival.	
Objectives and endpoints: Phase 1b		
Primary	**Objectives**	**Endpoints**
	Determine the recommended Phase 2 dose (RP2D) of this combination in patients with metastatic ER+, PgR+, HER2- breast cancer.	Number of dose-limiting toxicities (DLTs) observed during the first cycle.
Secondary	Characterize the safety of elacestrant in combination with onapristone.	AEs and serious adverse events (SAEs) as well as changes in clinical laboratory values, vital sign measurements and ECG parameters.
	Evaluate the plasma pharmacokinetics (PK) of elacestrant as well as onapristone and their metabolites.	Standard plasma PK parameters including, but not limited to, the area under the plasma concentration-time curve over the dosing interval ($AUC_{0\text{-}tau}$), C_{max}, time of the maximum observed plasma concentration (T_{max}), and C_{trough}.
	Evaluate the efficacy of elacestrant in combination with onapristone, in terms of objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1, duration of response (DoR), clinical benefit rate (CBR), progression-free survival (PFS), and overall survival (OS).	ORR: proportion of patients achieving a best overall response of confirmed partial or complete response (PR+CR) DoR: time from the date of the 1st documented CR/PR until 1st documentation of disease progression or death, whichever comes first. CBR: proportion of subjects achieving a best overall response of confirmed partial or complete response, or

	All efficacy analysis will be done for all patients and according to *ESR1* mutation status.	durable stable disease (duration is at least 23 weeks). PFS: time from the date of the 1st dose to the date of the 1st documentation of disease progression or death, whichever occurs 1st. OS: time from 1st dose date to the date of death from any cause.
Exploratory	Assess the pharmacodynamics (PD)	Changes in allele mutation frequencies in cell-free nucleic acid (cfNA) in blood.
	Evaluate relationship between efficacy and PD	Relationship between efficacy endpoints and allele mutation frequencies (at baseline and post baseline).
	Evaluate the efficacy of the combination according to *ESR1* mutation status	ORR, DoR, CBR, PFS, and OS
	Evaluate the efficacy of the combination according to the levels of the PgR	ORR, DoR, CBR, PFS, and OS
Objectives and endpoints: Phase 2		
Primary	**Objectives**	**Endpoints**
	Evaluate the efficacy of elacestrant in combination with onapristone, in terms of objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1. All efficacy analysis will be performed for all patients and according to *ESR1* mutation status.	ORR
Secondary	Evaluate the efficacy of elacestrant in combination with onapristone, in terms of DoR, CBR, PFS, and OS.	DoR, CBR, PFS, OS
	Further characterize the safety of elacestrant, in combination with onapristone at the RP2D.	AEs and SAEs as well as changes in clinical laboratory values, vital sign measurements and ECG parameters.

Exploratory	Assess the PD of each combination	Changes in biomarkers including, but not limited to, allele mutation frequencies in cfNA in blood.
	Evaluate relationship between efficacy and PD	Relationship between efficacy endpoints and allele mutation frequencies (at baseline and post baseline).
	Evaluate the efficacy of the combination according to *ESR1* mutation status	ORR, DoR, CBR, PFS, and OS
	Evaluate the efficacy of the combination according to the levels of the PgR	ORR, DoR, CBR, PFS, and OS
Eligibility Criteria		
Inclusion	1. Women or men aged ≥18 years, at the time of informed consent signature. *Note:* Pre- and peri-menopausal women must receive goserelin for at least one month prior to initiating trial therapy, during the trial, and for at least one month after end of trial therapy. Men must receive triptorelin for at least one month prior to initiating trial therapy, during the trial and for at least one month after end of trial therapy. 2. Histopathologically or cytologically confirmed ER+, PgR+, HER2-, breast cancer, per local laboratory, as per the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines (Allison *et al*, 2020). *Note*: In the context of this trial, ER and PgR status will be considered positive if ≥10% of tumor cells demonstrate positive nuclear staining by immunohistochemistry. 3. At least one measurable lesion as per RECIST version 1.1. *Note*: Patients with stable brain or subdural metastases are allowed if the patient has completed local therapy and has discontinued the use of corticosteroids for at least 4 weeks before starting treatment in this study. Any signs (e.g., radiologic) or symptoms of brain metastases must be stable for at least 4 weeks before starting study treatment. 4. Prior therapy with an aromatase inhibitor or fulvestrant + a CDK4/6 inhibitor in the metastatic setting or in the adjuvant setting if within 12 months of last dose of adjuvant therapy. *Note:* Prior therapy with everolimus is allowed. 5. ECOG performance status of 0 or 1. 6. Patient has adequate bone marrow and organ function, as defined by the following laboratory values: a. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L	

	b. Platelets ≥100 × 10^9/L c. Hemoglobin ≥9.0 g/dL d. Potassium, sodium, calcium (corrected for serum albumin), and magnesium CTCAE grade ≤1 e. Cockcroft-Gault-based creatinine clearance ≥50 mL/min. *Note:* Creatinine clearance (male) = ([140-age in years] × weight in kg)/ ([serum creatinine in mg/dL] × 72) Creatinine clearance (female) = (0.85 × [140-age in years] × weight in kg)/ ([serum creatinine in mg/dL] × 72) f. Serum albumin ≥3.0 g/dL (≥30 g/L) g. In absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3.0 × ULN. If the patient has liver metastases, ALT and AST ≤5 × ULN h. Total serum bilirubin <1.5 × ULN except for patients with Gilbert's syndrome who may be included if the total serum bilirubin is ≤3.0 × ULN or direct bilirubin ≤1.5 × ULN.
Exclusion	1. Active or newly diagnosed CNS metastases, including meningeal carcinomatosis. 2. Breast cancer treatment-naïve patients in the metastatic setting. 3. Prior therapy with elacestrant, onapristone, or chemotherapy in the metastatic setting. 4. Patient has a concurrent malignancy or history of invasive malignancy within 3 years of enrollment, with the exception of basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix that has completed curative therapy. 5. Uncontrolled significant active infections. a. Patients with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infection must have undetectable viral load during screening. b. Patients known to be HIV+ are allowed as long as they have undetectable viral load at baseline. 6. Major surgery within 4 weeks before starting trial therapy. 7. Inability to take oral medication, or history of malabsorption syndrome or any other uncontrolled gastrointestinal condition. 8. Females of childbearing potential who: a. Within 28 days before study entry, did not use a highly effective method of contraception. b. Do not agree to use a highly effective method of contraception throughout the entire study period and for 28 days after trial therapy discontinuation. 9. Males who do not agree to abstain from donating sperm, or to use a highly effective method of contraception, during the course of the treatment period and for 28 days thereafter.

	10. Known intolerance to either study drug or any of the excipients. 11. Patient is currently receiving or received any of the following medications prior to first dose of trial therapy: a. Known strong or moderate inducers or inhibitors of cytochrome P450 (CYP) 3A4 within 14 days or 5 half-lives, whichever is shorter, (Refer to http://medicine.iupui.edu/clinpharm/ddis/), b. Herbal preparations/medications within 7 days. These include, but are not limited to, St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. c. Investigational anti-cancer therapy with 21 days or 5 half-lives, whichever is shorter. d. Vaccination, including but not limited to vaccination against COVID-19, during the 7 days prior to randomization. 12. Evidence of ongoing alcohol or drug abuse.
Investigational Product, Dosage, and Mode of Administration	The combination of elacestrant and onapristone evaluated in this study is considered experimental in this patient population. Elacestrant dihydrochloride will be supplied as 100 mg and 400 mg (equivalent to 86 mg and 345 mg of elacestrant free base, respectively) tablets for oral administration. Elacestrant will be administered orally QD. Onapristone will be available as 10 mg, and 20 mg tablets and will be administered orally BID. Patients receiving both drugs should take elacestrant with onapristone at the same time in the morning every day. Both drugs should be taken with light food and a glass of water. In the context of this clinical trial, one cycle will be defined as 4 weeks (28 days).
Duration of Study:	The study duration for each patient is estimated to be: • Screening Phase: Up to 21 days prior to Cycle 1, Day 1. • Treatment Phase: From Cycle 1, Day 1 until the date of treatment discontinuation for any reason. • Survival Follow-Up Phase: All patients will be followed for survival approximately every 3 months for up to 24 months after enrollment of the last patient. Patients will be followed for AEs for 28 days after the last treatment administration. Patients who discontinue 1 of the 2 drugs and continue therapy with the other drug are considered 'on treatment' until they discontinue the second drug.
Criteria for Evaluation:	Efficacy: RECIST version 1.1 (Eisenhauer *et al*, 2009) Safety: NCI CTCAE version 5.0 (CTCAE v5.0, 2017).
Treatment duration	Treatment will continue until disease progression, death, development of unacceptable toxicity, withdrawal of consent, or other reasons.

	Average treatment duration is estimated to be 6 months.
End of Study	The cutoff date for the main analysis will be approximately 6 months after enrollment of the last patient. The cutoff date for an updated analysis, including OS, will be approximately 24 months after enrollment of the last patient. The study will be closed within 6 months of the cutoff date for the survival analysis.
Study Design	This study has 2 phases: a Phase 1b testing elacestrant in combination with onapristone, followed by a Phase 2 evaluation of the combination in women and men with advanced/metastatic ER+, PgR+, HER2- breast cancer.
Phase 1b	This phase will have between 1 and 4 cohorts of 6 patients each. The doses of 100 mg, 200 mg, 300 mg, and 400 mg of elacestrant dihydrochloride correspond to the doses of 86 mg, 173, 258 mg, and 345 mg of elacestrant free base, respectively. Cohort 1 will evaluate the combination of elacestrant dihydrochloride at a starting dose of 200 mg once daily (QD) in combination with onapristone at a starting dose of 40 mg twice daily (BID). • If ≤1 patient experiences a dose-limiting toxicity (DLT) during the first cycle (28 days), enrolment to Cohort 2 will be initiated. • If ≥2 patients experience a DLT, the combination at the doses evaluated at Cohort 1 will be considered not feasible and the Study Steering Committee (SSC) may decide to test lower doses based on all available data including safety, PK, and PD. Cohort 2 will evaluate the combination of elacestrant dihydrochloride at a starting dose of 300 mg once daily (QD) in combination with onapristone at a starting dose of 40 mg twice daily (BID). • If ≤1 patient experiences a DLT during the first cycle, enrolment to Cohort 3 will be initiated. • If ≥2 patients experience DLTs in the second cohort, the doses evaluated in Cohort 1 will be considered the recommended phase 2 dose (RP2D) of this combination. Cohort 3 will evaluate the combination of elacestrant dihydrochloride at a starting dose of 400 mg QD with onapristone at a starting dose of 40 mg BID. • If ≤1 patient experiences a DLT during the first cycle, enrolment to Cohort 4 will be initiated. • If ≥2 patients experience DLTs, the doses evaluated in Cohort 2 will be considered the recommended phase 2 dose (RP2D) of this combination. Cohort 4 will evaluate the combination of elacestrant dihydrochloride at a starting dose of 400 mg QD with onapristone at a starting dose of 50 mg BID. • If ≤1 patient experiences a DLT during the first cycle, the doses evaluated at this cohort will be considered the RP2D for this combination.

<table>
<tr><td></td><td>

- If ≥2 patients experience DLTs, the doses evaluated in Cohort 3 will be considered the RP2D of this combination.

</td></tr>
<tr><td>Phase 2</td><td>Eligible patients will receive the combination of elacestrant and onapristone at the RP2D determined during the phase 1b part of the trial.</td></tr>
<tr><td>Definition of DLT</td><td>Dose-limiting toxicity (DLT) is based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). DLT refers to toxicities experienced during Cycle 1 by patients enrolled in the Phase 1b part of the trial.
Any of the following toxicities that is not clearly due to breast cancer or extraneous causes will be considered a DLT:
<table>
<tr><th>Toxcicity</th><th>Criteria</th></tr>
<tr><td>Hematology</td><td>• Febrile neutropenia
• Grade 4 neutropenia that does not resolve to Grade ≤3 within 8 days
• Grade 4 thrombocytopenia
• Grade 3 thrombocytopenia lasting >8 days</td></tr>
<tr><td>Fatigue</td><td>• Grade 3 or 4 lasting for ≥7 days</td></tr>
<tr><td>Nausea</td><td>• Grade 3 lasting >72 hours despite optimal antiemetic treatment</td></tr>
<tr><td>Vomiting</td><td>• Grade 4
• Grade 3 lasting >72 hours despite optimal antiemetic treatment</td></tr>
<tr><td>Diarrhea</td><td>• Grade 4 diarrhea
• Grade 3 lasting >72 hours despite optimal antidiarrheal treatment</td></tr>
<tr><td>Electrolytes</td><td>• Grade 3 or 4 associated with clinical signs and symptoms, regardless of duration</td></tr>
<tr><td>Renal</td><td>• Grade 3 or 4 serum creatinine increase</td></tr>
<tr><td>Hepatic</td><td>• Grade 3 or 4 bilirubin increase
• ALT or AST ≥10 × ULN</td></tr>
<tr><td>Hy’s law</td><td>• ALT or AST >3 × ULN with bilirubin >2 × ULN in the absence of viral hepatitis A, B or C; preexisting or acute liver disease, or another drug causing the observed injury</td></tr>
<tr><td>Biochemistry</td><td>• Grade 4
• Grade 3 lasting >8 days, unless considered not clinically significant as per the discretion of the investigator</td></tr>
</table>
</td></tr>
</table>

	Other non-hematological	• Grade 3 or 4
	Death	• Not clearly due to underlying disease or extraneous causes
Sample Size		
Phase 1b	The Phase 1b aims at selecting the RP2D dose, defined as a dose that is associated with less than 33% of patients experiencing a DLT, that is, ≤1 patient experiencing a DLT out of 6 DLT-evaluable patients. Patients who receive <70% of the scheduled therapy during Cycle 1 of either drug, for reasons other than toxicity, will not be considered evaluable for DLT assessment and will be replaced. Disease progression and adverse events (AEs) deemed related to disease progression will not be considered DLTs. The Phase 1b will have between 6 and 24 DLT-evaluable patients.	
Phase 2	A Simon two-stage design (Simon, 1989) will be used to evaluate the ORR in the Response-Evaluable Set (RES). The null hypothesis that the true RR in the RES is 5% will be tested against a one-sided alternative of 20%. Among the first 21 response-evaluable patients, if there is no or only one confirmed response, enrollment will be stopped. This futility analysis will be performed approximately 16 weeks after enrollment of the 21st patient. If there are 2 or more objective responses in these 21 patients, additional patients will be accrued in order to have a total of 41 response evaluable patients. Patients treated at the RP2D in the Phase 1b part of the trial will be counted as part of the Phase 2 patients. While accumulating data from stage 1, enrollment into stage 2 may be continued or held depending on agreement between the SSC and the Sponsor. By the end of the study, if there are 5 or more objective responses in 41 response-evaluable patients, the null hypothesis will be rejected, and the treatment evaluated in this arm will be considered active in this patient population. This design yields a type I error of 0.05 (one-sided) and power of 90% with the true RR of 20%. Patients who are not deemed response-evaluable will be replaced. It is anticipated that this category will not exceed 10%, that is, approximately 4 additional patients. The total number of phase 1 and phase 2 patients will be approximately 67. It is estimated that approximately 40% of all patients will have tumors harboring *ESR1* mutations. After enrolling approximately 40 patients, a review of *ESR1* mutation status will be performed and enrollment may be restricted to patients with *ESR1* mutations in order to allow for meaningful assessment of efficacy in this group of patients.	
Analysis Sets	Except for the DLT analysis set that will only apply for the Phase 1b part of the trial, all other analysis sets will be defined separately for the Phase 1b and the Phase 2 parts of the study. • DLT Analysis Set: all patients who start trial therapy unless they receive <70% of their scheduled therapy during the first cycle for reasons other	

	than toxicity. Any patient who experiences a DLT will also be considered evaluable, irrespective of the percentage of scheduled therapy received during the first cycle. Patients enrolled in the Phase 1b who are not DLT evaluable will be replaced. • Safety Analysis Set (SAS): All patients who receive at least 1 dose of elacestrant or onapristone. This will be the analysis set for all safety evaluations. • The Intention-to-Treat (ITT) Set: In the context of this trial, the ITT population is the same as the SAS. This will be the analysis set for PFS and OS. • Response-Evaluable Set (RES): Includes patients in the SAS who have a baseline radiological tumor assessment and at least one post-baseline radiological tumor assessment taken at least 42 days after Cycle 1, Day 1. This will be the primary analysis set for efficacy assessments, excluding PFS and OS. • Pharmacokinetic Analysis Set: Includes patients in the SAS who have reliable drug assay data relevant for the PK analysis.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
β-hCG	beta-human chorionic gonadotropin
BCRP	breast cancer resistance protein
BID	Twice daily
BP	blood pressure
CA	Competent Authority
CAS	Chemical Abstracts Services
CBC	complete blood cell (count)
CBR	clinical benefit rate
cfNA	cell-free nucleic acid
CFR	Code of Federal Regulations
CL/F	apparent total body clearance following oral administration
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CR	complete response
CRF	case report form
CRA	clinical research associates
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	curriculum vitae
CYP	cytochrome P450
DCR	disease control rate
DDI	drug-drug interaction
DHEA	dehydroepiandrosterone
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response
EC	Ethics Committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
ER	estrogen receptor
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor-2

Abbreviation	Term
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	international normalized ratio
IMP	Investigational Manufacturing Product
IRB	institutional review board
IV	intravenous
LMWH	low-molecular-weight heparin
LVEF	left ventricular ejection fraction
MATE	multidrug and toxin extrusion transporter
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	multiple-gated acquisition
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NaF PET	^{18}F-sodium fluoride position emission tomography
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic(s)
PFS	progression-free survival
P-gp	P-glycoprotein
PI	principal investigator
PK	pharmacokinetic(s)
PO	orally
PR	partial response
PT	preferred term
PT/PTT	prothrombin time/partial thromboplastin time
QD	once daily
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RANKL	receptor activator of nuclear factor kappa-B ligand
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RES	Response-Evaluable Set
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SSC	Study Steering Committee
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
TEAE	treatment-emergent adverse event

Abbreviation	Term
T_{max}	time of maximum observed plasma concentration
ULN	upper limit of normal
US	United States
WHO DD	World Health Organization Drug Dictionary

3 BACKGROUND AND RATIONALE

3.1 Epidemiology

The incidence and prevalence of patients with invasive breast cancer in females, as well as estimates for the prevalence of patients with ER+, PgR+, HER2- breast cancer are presented in Table 1.

Table 1: Epidemiology of ER+ HER2- Breast Cancer (× 1000)

	US	EU	Japan	Global
Incidence: new yearly cases of invasive BC	288[a], 253[b]	531[b]	92[b]	2,261[b]
Prevalence	1,071[b]	2,138[b]	329[b]	7,791[b]
Prevalence of ER+, HER2- BC (~70% of invasive BC)	750	1,497	230	5,454
Prevalence of ER+, PgR+, HER2-BR (~85-90% of ER+, HER2- BC)[c]	656	1,301	201	4,772

BC = breast cancer, ER = estrogen receptor, EU = European Union, HER2 = human epidermal growth factor receptor-2, US = United States

a. National Cancer Institute, Surveillance, Epidemiology, and End Results (SEER) Program, 2022.
b. International Agency for Research on Cancer, World Health Organization, Global Cancer Observatory https://gco.iarc.fr/ accessed August 7, 2022.
c. Fei *et al*, 2017.

3.2 Current Treatments and Unmet Medical Need

The addition of a CDK 4/6 inhibitor to hormonal therapy, as a first or second line therapy, provided a significant improvement in PFS, and in some cases in OS, with a tolerable toxicity profile, and is, therefore, the preferred treatment options for patients with ER-positive, HER2-negative advanced breast cancer (Turner *et al*, 2018; Finn *et al*, 2016a; Finn *et al*, 2016b; Cristofanilli *et al*, 2016; Johnston and Martin, 2019; Slamon *et al*, 2020). However, acquired resistance to this combination remains a challenge (O'Leary *et al*, 2018; Haque and Desai, 2019; Bessone *et al*, 2019). There is currently no evidence to support continuing the same CDK4/6 inhibitor or switching to a different CDK4/6 inhibitor after progression.

Recently, alpelisib, a PI3K inhibitor, was approved in combination with fulvestrant for the treatment of PIK3CA-mutated, mBC, based on the SOLAR-1 trial data. Hyperglycemia, and diarrhea were main side effects of alpelisib, and 25% of the study patients discontinued alpelisib due to adverse effects (André *et al*, 2019).

Regardless, most patients progress on these agents and ultimately develop endocrine resistance, thus, emphasizing the critical need for novel treatments.

The purpose of this study is to evaluate the safety and efficacy of elacestrant in combination with onapristone extended release in women with ER+, PgR+, HER2- advanced or metastatic breast cancer which progressed on or after prior therapy with a CDK4/6 inhibitor.

3.3 Progesterone and Progesterone Receptor

The progesterone receptor (PgR) has long been used clinically as a biomarker of ER transcriptional activity and as an indicator of sensitivity to antiestrogens. However, studies from the past two decades show that PgR strongly modulates ER activity in breast cancer, while also being an independent, context-dependent, driver of ER+ breast cancer phenotypes associated with tumor progression in vitro, ex vivo, and in vivo (De Amicis *et al*, 2009; Mohammed *et al*, 2015; Daniel *et al*, 2015; Singhal *et al*, 2016; Knutson *et al*, 2017).

The PgR gene is well-studied as an estrogen-responsive gene that is upregulated by the ER in response to the estrogen stimulation of ER+ tissues, including the uterus and breast. For this reason, PgR is used as a clinical biomarker of estrogen signaling during breast cancer diagnosis and signifies the presence of a functional ER in tumor cells. Breast cancers with high levels of both ER and PgR (luminal A type) respond well to endocrine therapy. In contrast, luminal B type breast cancers exhibit lower levels of ER and little to no PgR protein expression (ER+/PgR-low/null). Such luminal B cancers are more likely to be endocrine resistant at diagnosis or may rapidly become endocrine resistant during disease progression (Rojas *et al*, 2017; Dwyer *et al*, 2020). ER and PgR seldom function independently in breast cancer cells; PgR-A can inhibit ER actions while PgR-B can be an important ER binding partner (PgR-B), helping to regulate numerous estrogen-regulated genes via both direct and indirect receptor crosstalk (Mohammed *et al*, 2015; Singhal *et al*, 2016; Truong and Lange, 2018; Dwyer *et al*, 2021; Paakinaho and Palvimo, 2021).

3.3.1 Mechanism of Action

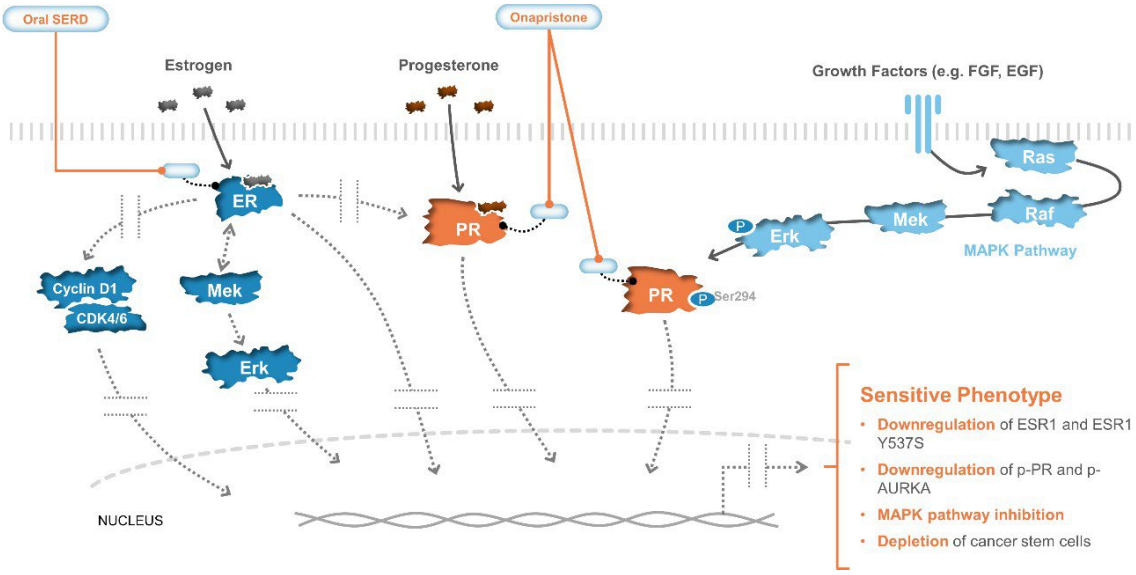
The PgR is expressed as two main forms (PgR-A and PgR-B) with different molecular weights and functions. PgR-A is mainly localized in the nucleus, whereas PgR-B continuously shuttles between nuclear and cytoplasmic compartments (Scarpin *et al*, 2009). In normal human tissues, expression of PgR-A and PgR-B is balanced, while in malignant tissues, the proportion of PgR-A and PgR-B may be greatly altered: PgR isoform predominance, especially PgR-A predominance, is evident in a significant proportion of ductal carcinoma in situ (DCIS) and invasive cancers. Another distinctive feature of malignancy is that there is marked heterogeneity of PgR-A:PgR-B expression between neighboring cells, as demonstrated in breast and endometrial cancers (Mote and Clarke, 2000; Arnett-Mansfield *et al*, 2004; Sasaki *et al*, 2002; Scarpin *et al*, 2009).

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.

Upon ligand-dependent or ligand-independent activation, PgR-A and PgR-B form homodimers or heterodimers that exhibit distinct transcriptional regulatory functions. PgR-B can mediate either direct, nuclear transcriptional events or rapid cytoplasmic changes by interacting with non-nuclear signaling pathways, such as mitogen-activated protein kinase (MAPK), c-Src, PI3K/Akt, and Janus kinase 2 (Faivre and Lange, 2007; Hagan *et al*, 2011; Gupta and Mayer, 2013). It is likely that both isoforms elicit distinct and coordinated functions in both the nuclear and cytoplasmic compartments (reviewed in Hilton *et al*, 2015; Knutson *et al*, 2017).

Upon ligand binding, the PgR dimerizes and attracts nuclear cofactors to form a complex. This complex becomes functional and binds to specific DNA promoter sequences of PgR-dependent genes, termed Progesterone Response Elements (PREs). A simplified diagram of the proposed mechanism of transcriptional activation of the PgR is illustrated below in Figure 1.

Figure 1: Proposed model of activated PgR



The turnover of unliganded PgR in cells is roughly 20-22 hours, while phosphorylated PgRs have a much shorter half-life, on the order of minutes to an hour when PgR Ser294 is phosphorylated. Thus, when PgR is phosphorylated and active, and when PgR target gene products are high the PgR protein is often undetectable by standard Western or IHC-based protocols.

3.3.2 Progesterone Promotes Cancer Cell Proliferation

Recent studies indicate that Pg promotes mammary tumorigenesis (Lanari *et al*., 2009; Lange, 2008). Evidence includes that: a) administration of medroxyprogesterone acetate, a synthesized progesterone, induces mammary ductal carcinomas BALB/c female mice (Lanari *et al*, 2009), b) Pg has proliferative effects in the PgR-positive breast cancer cell lines in vitro (Hissom and Moore, 1987; Liu *et al*, 2011) and in nude mice (Liang *et al*, 2007); c) PgR phosphorylation at Ser294 was strongly induced by progesterone treatment and is associated with increased Ki67 (O'Leary *et al*, 2018). Clinically, in several large-scale hormone replacement therapy studies, Pg plus estrogen significantly increased the risk of invasive breast cancer compared with estrogen alone (Beral *et al*, 2003; Kirsh and Kreiger, 2002; Schairer *et al*, 2000).

PgR expression in breast cancer predicts response to ER-targeted therapies, in part because ER is a primary regulator of PgR expression (Musgrove and Sutherland, 2009). Progesterone dependent and progesterone independent PgR actions include scaffolding of growth factor pathways to enhance kinase signaling (Proietti *et al*, 2009) and activation of pro-growth and pro-survival transcriptional programs in breast cancer cells (Daniel and Lange, 2009; Hagan *et*

al, 2011; Knutson *et al*, 2012).

Progesterone alone was a potent stimulator of proliferation in ex vivo breast tumor tissue samples, while estrogen was a weak stimulator (Lanari *et al*, 2012; Knutson *et al*, 2017). In vitro studies of antiprogestins using breast cancer cell lines and in vivo rodent models demonstrated that PgRs drive tumor cell proliferation and that this effect is antagonized by PgR antagonists or PgR silencing (Michna, *et al*, 1989: reviewed in Lanari *et al*, 2012). Of note is that both mifepristone- and onapristone-induced antitumor activity appears to be the result of direct PgR -mediated antiproliferative effects at the level of the mammary tumor cells, most probably via the induction of terminal differentiation associated with terminal cell death (apoptosis) (Michna *et al*, 1992; Gaddy *et al*, 2004).

A key driver of cell proliferation in human breast cancer tissue is RANKL (receptor activator of nuclear factor kB ligand), which has been identified to be under PgR control (Tanos *et al*, 2013; Renema *et al*, 2016; Ming *et al*, 2020; Wu *et al*, 2020). Consistent with this finding the PgR antagonist, CDB-2914, inhibited cell cycle progression in aromatase inhibitor-resistant breast cancer cells (Gupta, *et al*, 2013).

PgR-B induces robust expression of a subset of estradiol-responsive ER-target genes, including Cathepsin D (CTSD), which participates in tumor cell proliferation. Knockdown of endogenous PgR or onapristone treatment of multiple breast cancer cell lines blocked estradiol-mediated CTSD induction, inhibited tumor cell growth, and partially restored tamoxifen-sensitivity of resistant cells (Daniel *et al*, 2015). The PgR antagonist, ulipristal acetate has also been shown to inhibit breast cancer cell proliferation in an ERα-independent fashion (Esber *et al*, 2015).

In addition to ligand-activated transcription, phosphorylation of PgR via growth factor mediated kinases is associated with transcriptional hyperactivity at PgR target genes that are important for breast cancer cell proliferation and survival (Knutson *et al*, 2017). Growth factor activity may reduce or supplant the need for a progestin ligand and leads to ligand-independent activation of PgR.

PgR signaling interacts with ER signaling to drive sustained tumor cell proliferation, as well as tumor cell survival (Giulianelli *et al*, 2012). PgR can modulate ER binding sites and transcriptional activity, and selective PgR modulator drugs can synergize with tamoxifen to cause tumor regression in mice (Mohammed *et al* 2015; Singhal *et al*, 2016; Daniel *et al*, 2015; Finlay-Schultz *et al*, 2017; Konan *et al*, 2020). PgR dramatically impacts ER action in breast cancer, with data showing improved response to ET with ER+/PgR+ compared with ER+/ PgR- breast cancer (Parise and Caggiano, 2014; Mohammed *et al*, 2015; Nordenskjöld *et al*, 2016). ER/PgR crosstalk is further discussed, below.

Together, the evidence for PgR contributions to tumor cell proliferation indicate that estrogen/ER blockade, by itself, may be insufficient for a maximal anti-proliferative effect, and that the addition of PgR blockade may enhance the suppression of tumor cell proliferation.

In summary, progesterone has emerged as a key mediator of both normal and neoplastic mammary gland stem cell expansion (Knutson *et al*, 2017). As a consequence, the PgR is

considered a relevant therapeutic target for further study in breast cancer (Hagan *et al*, 2011; Faivre and Lange, 2007; Scarpin *et al*, 2009; Jonat *et al*, 2013). PgR activation in breast cancer provides a strong rationale for the use of antiprogestins, in particular onapristone, that can antagonize both ligand-independent and ligand-dependent PgR activity for the treatment of breast cancer.

3.3.3 Progesterone Drives Metastatic Spread in Breast Cancer

Progesterone supports invasiveness and metastasis in luminal breast cancer cells (Liang *et al*, 2007; Liang *et al*, 2010). Mechanistic studies suggest that hormonal crosstalk of PgR-A with ER enables metastasis of luminal breast cancer (McFall *et al*, 2018; Rosati *et al*, 2020). Further, PgR activity is strongly implicated in breast cancer metastatic progression by increasing invasiveness of primary cancer cells through transcriptional regulation of key proteins involved in cellular migration and adhesion, such as matrix metalloproteases (MMPs), vascular endothelial growth factor, the plasminogen activator (PA) system, and focal adhesion kinase (Bellance *et al*, 2013). Overall, data suggest that PgR-induced signaling is a key driver of metastatic migration (dissemination) of cancer cells from tumors. Recent data further suggests that the majority of metastases are derived from early disseminated cells, as opposed to metastatic seeding from advanced tumors (Hosseini *et al*, 2016).

3.3.4 Progesterone Supports Immune Evasion

Current immunomodulatory therapies include immune checkpoint blockade (ICB), dendritic cell (DC)-based, and adoptive T cell transfer. Patients treated with ICB have shown durable increased overall survival and progression-free survival responses in a variety of tumors (reviewed in Robert 2020). However, immunotherapy implementation for breast cancer has been particularly challenging. This is because mammary carcinomas were traditionally considered immunologically “cold” because of their scant or null T cell infiltration (a negative predictor for response to ICB) (reviewed in Adams *et al*, 2019).

Recently, multiple studies have been published demonstrating that progesterone or overexpression of PgR result in changes that may inhibit immune responses in the murine mammary gland, lymph nodes and other tissues. Mice overexpressing PgR develop an increased number of mammary gland tumors compared with control mice. In addition, tumors of PgR-overexpressing mice exhibit fewer infiltrating lymphocytes and decreased immune gene expression signatures compared with tumors of control mice. The effects of PgR and progesterone on the immune system and subsequent tumor growth are likely mediated through direct actions/released factors from PgR-positive tumor cells, as PgR-negative tumor cells did not elicit a similar immune response (Werner *et al*, 2021). Further work has shown that PgR signaling can block an interferon (IFN) signaling cascade that is critically involved in immune recognition and destruction of nascent tumor cells. Downregulation of this IFN pathway promotes a more immunosuppressed microenvironment that contributes to luminal breast cancer cell immune evasion (Walter *et al*, 2017; Walter *et al*, 2020; Goodman *et al*, 2019). Importantly, treatment with onapristone reverses the PgR-driven IFN blockade – suggesting that antiprogestin therapy may represent a novel therapeutic strategy for promoting immune

activity within the tumor (Walter *et al*, 2020). Consistent with this work have been parallel findings that antiprogestin (mifepristone) therapy induces immunogenic tumor cell death in PRA-overexpressing tumors, eliciting an adaptive immune memory response that protects mice from future tumor recurrence and increases sensitivity to PD-L1 blockade (Sequeira *et al*, 2021).

These findings provide a rationale for targeting PgR in breast cancer as a mechanism to promote anti-tumor immune responses, possibly in conjunction with ICB.

3.3.5 Antiprogestins in Patients with Acquired *ESR1* Mutations

Recent data suggest that mutations in the *ESR1* gene encoding ERα play a significant role in resistance to endocrine therapy (Chandarlapaty *et al*, 2016; Nardone *et al*, 2015; O'Leary *et al*, 2018). Two commonly described mutations are Y537S and D538G. Y537S-specific *ESR1* mutations are reported as drivers of resistance to fulvestrant plus palbociclib combination therapy (O'Leary *et al*, 2018; Dustin *et al*, 2019). Even in the absence of estradiol, these acquired mutations can lead to the expression of constitutively active ER that promotes PgR expression that drives enhanced tumor cell proliferation (Kuang *et al*, 2018). Consistent with this finding, the Lange lab (unpublished results) has shown that knockdown of endogenous PgR in multiple *ESR1* mutant breast cancer models blocked anchorage-independent growth and mammosphere formation.

These data collectively suggest that blocking both ER and PgR signaling pathways with anti-ER/PgR based combination therapies could be a promising strategy in breast cancer patients who have acquired resistance after long-term ER inhibition—and especially in patients with the emergence of PgR-rich metastatic tumors harboring *ESR1* mutations (Kumar *et al*, 2021).

3.3.6 Progesterone Receptor Antisense

Several animal models have shown that antiprogestins were able to inhibit tumor growth as single agents. These models included tumor growth that was: a) progestin-induced; b) 7,12-dimethylbenz(α)anthracene (DMBA)-induced; c) estrogen-induced; and even in d) progestin-induced but progestin-growth independent tumors. It seems that 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 PgR were injected intraperitoneally with PgR antisense oligos every 24 or 12 hours for 5 or 10 days, respectively, or continuous mifepristone SC once every 24 hours or once as a SC implant. Control mice received vehicle or scrambled oligonucleotide to PgRs. Tumor growth was inhibited by PgR antisense oligos, onapristone and mifepristone; leading the authors to conclude that this provided further evidence for a critical and hierarchical role for the PgR pathway in mammary carcinomas (Montecchia *et al*, 1999; Lamb *et al*, 2005).

3.4 ER/PgR Crosstalk

ER/PgR crosstalk is the interplay between these receptors that can take place either directly or between their overlapping signaling pathways. ER/PgR crosstalk modulates signaling and

transcriptional responses to noncognate ligands (Migliaccio *et al*, 1998; Ballaréé *et al*, 2003; Boonyaratanakornkit *et al*, 2001; Boonyaratanakornkit *et al*, 2007; Giulianelli *et al*, 2012; Daniel *et al*, 2015; Mohammed *et al*, 2015; Truong and Lange, 2018). In other words, PgR activity could drive ER signaling in the absence of estradiol, while ER activity could drive PgR signaling in the absence of progesterone. In the context of hormone-dependent cancers, such as breast cancer, ER/PgR crosstalk can lead to alternative proliferation and survival signals that promote hormone independence which can lead to the emergence of resistance to ER-targeted therapies (Daniel *et al*, 2015; Truong and Lange, 2018; Dwyer *et al*, 2021).

Recent studies demonstrate that PgR is a binding partner and major modifier of ER actions, which has consequences for hormone-driven breast cancer growth and implications for endocrine therapy responses (Daniel *et al*, 2015; Mohammed *et al*, 2015; Singhal *et al*, 2016; Hegde *et al*, 2016; Finlay-Schultz *et al* 2017). PR and ER have been shown to associate in cytoplasm as well as at multiple DNA binding sites, including both progesterone and estrogen response elements (Truong and Lange, 2018). While the current section will focus on ER/PR crosstalk, it is important to keep in mind that genome-wide crosstalk among multiple steroid receptors has been implicated in various elements of tumorigenesis (Truong and Lange, 2018; Paakinaho and Palvimo, 2021; Kowalczyk *et al*, 2021). Examples of ER/PgR crosstalk in breast cancer are summarized below.

3.4.1 ER signaling to the ERK pathway in response to PR-B activation

The first mechanistic studies of ER/PgR crosstalk were reported in the context of rapid signaling cascades (kinase signaling) in hormone-treated breast cancer cell lines (Migliacco *et al*, 1998; Ballaréé *et al*, 2003). Progestins were shown to stimulate proliferation in human breast cancer cells by rapid induction of the c-Src/p21ras/Erk kinase signaling pathway mediated by cytoplasmic ER/PgR/c-Src complexes; proliferation was blocked using either antiprogestins or antiestrogens. It was found, in these studies, that PgR does not interact directly with c-Src, but rather with ER through direct interaction of two ER interaction domains located in the PgR N-terminus with an interaction domain on the ER. These studies provided the first evidence of ER/PgR crosstalk by which ER transmits signals to the c-Src/p21ras/Erk pathway in response to ligand-activated PR-B.

3.4.2 PgR-induced c-Src kinase activation requires ER activity

Conversely to the prior example of ER activity requiring PR-B co-activation, it was found that PR-B activation of c-Src kinase requires a coordinated ER/PgR proliferative signal that activates MAPK signaling (Migliacco *et al*, 1998; Boonyaratanakornkit *et al*, 2001; Boonyaratanakornkit *et al*, 2007).

3.4.3 ER/PgR crosstalk enables progestin-induced cell proliferation

Giulianelli *et al* (2012) reported that ER and PgR co-associated at target gene promoters to drive progestin-induced cell proliferation in cancer cell models. They further demonstrated that ER and PgR interact directly at chromatin to coregulate PgR-target gene expression and PR-mediated cancer cell proliferation. Taken together with the prior two examples of ER/PgR

crosstalk effects on kinase activation, the Giulianelli findings indicated that ER/PgR crosstalk appears to occur in both rapid signaling (kinase) and transcriptional contexts to impact gene expression and breast cancer cell fate (Giulianelli *et al*, 2012).

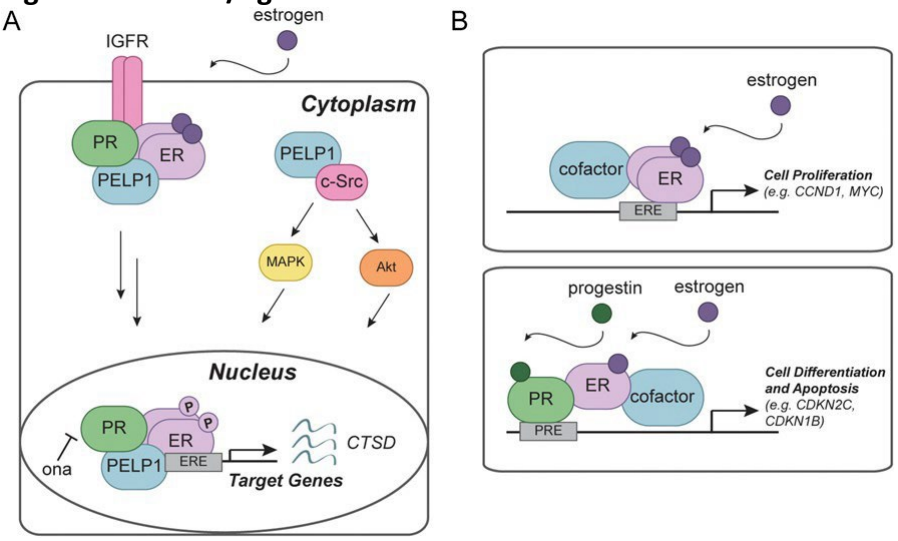
3.4.4 ER/PgR crosstalk in metastasis

Mechanistic studies suggest that hormonal crosstalk of PgR-A with ER enables metastasis of luminal breast cancer, notably by opposing regulation of critical microRNAs by estrogen (McFall *et al*, 2018; Rosati *et al*, 2020).

3.4.5 ER/PgR pairs can drive oncogenic gene programs

Studies from the Lange laboratory (Daniel *et al*, 2015) reported PgR-dependent regulation of ER target gene sets associated with endocrine resistance (Figure 2-A). In ER+ luminal breast cancer models, PgR-B was shown to participate in estrogen-induced ER signaling and transcriptional complexes independent of exogenously added progesterone. This constitutive complex, comprised of ERα, PgR-B, and the coactivator and scaffolding molecule PELP1, was observed in human breast tumor samples and multiple breast cancer cell lines. The consequences of this interaction in the presence of estrogen included enhanced ER phosphorylation, increased cellular proliferation, decreased sensitivity to tamoxifen treatment, and altered ER promoter selectivity (Figure 2-A). Global gene expression analysis of estrogen-treated ER+ breast cancer cells revealed that the presence of PgR-B (but not progestin) was required for estrogen induction of gene expression on select promoters (e.g., CTSD) previously thought to be entirely ER driven. Notably, PgR antagonists (onapristone) or PR knockdown blocked expression of these ER target genes. Taken together, these studies (Daniel *et al*, 2015; Giulianelli *et al*, 2012) demonstrated that breast cancer cells harboring both ER and PgR-B may be sensitive to estrogen or progesterone, alone. It is possible that ER and PgR can substitute functionally for each other via crosstalk (Truong and Lange, 2018). Utilization of ER-PgR protein-protein interactions (i.e., a form of sensing alternative ligands) allows ER/PgR pairs to drive oncogenic gene programs and thereby escape inhibition of one receptor type to promote endocrine resistance (Truong and Lange, 2018). For example, in metastatic tumors unresponsive to antiestrogen therapy, complexes consisting of the scaffold protein PELP1, along with ER and PgR-B have been identified and that PgR-B in such complexes can drive cell proliferation, thereby compensating for ER inhibition, driving cell proliferation (Daniel *et al*, 2015).

Figure 2: ER/PgR crosstalk in breast cancer



(A) PELP1, ER, and PgR-B form a constitutive signaling and transcriptional complex. PgR-B expression, but not progestin, is required for estradiol (E2) stimulated regulation of ER/PgR/PELP1 target genes (e.g., CTSD) associated with breast cancer progression to endocrine resistance. Onapristone (PgR antagonist) blocked expression of these estradiol-driven target genes (Daniel *et al*, 2015).
(B, top) estradiol-stimulated ER recruits cofactors within the genome to activate target genes that promote cell proliferation (Mohammed *et al*, 2015).
(B, bottom) Progesterone (P4)-stimulated PgR interacts with and reprograms estradiol-stimulated ER to novel binding sites that contain progesterone response elements (PREs). Target gene expression is shifted away from proliferation and toward a new profile associated with cell differentiation and apoptosis (Mohammed *et al* 2015).
ERE = estrogen response element; PRE= progesterone response element; IGFR = IGF receptor; IGF = insulin-associated growth factor.
Source: Truong and Lange, 2018.

Large-scale studies have recently confirmed that ER/PgR complexes mediate global changes in chromatin binding and ER-driven gene expression (Mohammed *et al*, 2015; Singhal *et al*, 2016).

Mohammed *et al* (2015) demonstrated that estradiol stimulated ER recruits co-factors to activate target genes that promote cell proliferation (Figure 2-B, top), but also reported that progesterone-stimulated PgR interacts with and reprograms estradiol-stimulated ER such that ER was shifted away from estrogen response elements (EREs) and onto progesterone-response elements (PREs; Figure 2-B, bottom) resulting in a shift from proliferative gene responses to cell differentiation and apoptosis.

As proposed by the Lange laboratory (Daniel *et al*, 2015), ER/PgR crosstalk establish a potential mechanism of escape from ER blockade. Given that estrogen or progesterone alone regulate

85% similar gene sets in breast cancer cell lines or primary breast tumor explants (Singhal *et al*, 2016), the potential for ER/PgR crosstalk to confound ER inhibitors/degraders indicates the potential importance of combined ER/PgR blockade in the treatment of ER+/PgR+ hormone-dependent cancers.

3.5 Combination Rationale

The purpose of this study is to evaluate the safety and efficacy of elacestrant in combination with onapristone (ONA-XR) in women with ER+, PgR+, HER2- breast cancer which progressed on or after prior therapy with a CDK4/6 inhibitor.

The key rationales for adding onapristone to elacestrant therapy are to:

1. Inhibit tumor cell growth and proliferation by inhibiting:
   - ER-driven (ER/PgR-driven) proliferation (via elacestrant) as well as, potentially, ER-independent, PgR driven proliferation that enables cells to escape from blockade of ER-driven proliferation (ER/PgR crosstalk effects).
   - PgR proliferative drive resulting from PgR induction by constitutively active ER in antiestrogen-resistant mutations.
2. Enhance tumor cell apoptosis by creating more complete cell cycle blockade than is possible with either single approach.

The hypothesis behind the current study is that adding PgR blockade to ER blockade will decrease tumor growth more than ER blockade, alone. The focus of progesterone and PgR research over the past two decades has been on how PgR activity affects transcriptional and signaling programs. This work, summarized above, has defined key roles for PgR activity in tumor cell proliferation, cancer stem cells (CSC) expansion, metastasis, invasiveness, and immune evasion as well as in proliferative activity in cells that have acquired resistance to ER blockade. These findings demonstrate that the PgR is far more than just a marker for the presence of active ER, and that it plays a critical role in tumorigenesis and metastasis. Empirical support for treating patients with joint ER-PgR blockade comes from both in vitro and in vivo models of ER positive tumors.

3.5.1 In Vitro Experiments

Thomas and Monet studied the combined effects of RU486 (mifepristone) and tamoxifen on the growth and cell cycle phases of MCF-7 human breast cancer cell line. This study found that at a treatment point (≤3 days), when RU486 or tamoxifen individually had no effect, the combination exhibited a synergistic inhibitory effect on cell proliferation (Thomas and Monet, 1992).

El Etreby *et al* (1998) studied the effect of mifepristone and tamoxifen, alone and in combination, in apoptotic pathways in MCF-7 cells. Mifepristone and tamoxifen, as mono-treatments, induced significant time- and dose-dependent inhibition of cell growth. Inhibition of cell survival was associated with a significant increase in DNA fragmentation (apoptosis). The effects of mifepristone plus tamoxifen on cell growth inhibition, DNA fragmentation, and other markers of cell survival was additive and significantly different ($P < 0.05$) from the effect of monotherapy. The results suggested that the additive antiproliferative activity of mifepristone and tamoxifen could be explained at least in part by an additive induction of apoptosis in both ER and PgR positive MCF-7 breast cancer cells (El Etreby *et al*, 1998).

Gaddy *et al* (2004) studied the effects of mifepristone and tamoxifen, alone and in combination,

on MCF-7 derived, clonal tumor cell lines with differing levels of tamoxifen resistance. The study evaluated the effects of ER and PgR blockade on cell growth (proliferation) and active cell death (apoptosis). Interestingly, the study demonstrated that ER+/PgR+ tamoxifen resistant cell lines could be isolated from an MCF-7 cell line in the absence of antiestrogen selection – meaning that spontaneous antiestrogen mutations were already present in the parent and that such ER-expressing antiestrogen-resistant variants might be present in human breast cancers prior to antiestrogen therapy. The study found that mifepristone, alone or in combination with tamoxifen induced growth arrest and cell death in antiestrogen-resistant, ER+/PgR+ MCF-7 cells. Importantly, the combination of ER plus PgR blockade induced growth arrest and cell death more effectively than either agent, alone (Gaddy *et al,* 2004).

Daniel *et al* (2015) studied the mechanisms of ER-PgR crosstalk underlying tumor cell proliferation in multiple unmodified breast cancer cell lines, as well as in cell lines with stable PgR knockdown. These researchers used genome-wide microarrays to reveal that PgR-B induces robust expression of a subset of estradiol-responsive ER-target genes, including Cathepsin D (CTSD), which participates in tumor cell proliferation. In multiple breast cancer cell lines, knockdown of endogenous PgR or onapristone treatment blocked estradiol-mediated CTSD induction, inhibited tumor cell growth, and partially restored tamoxifen-sensitivity of resistant cells. Importantly, these studies demonstrated that PgR-B and ER are both recruited to the CTSD promoter in order to drive estradiol-dependent CTSD transcription. That is, a key driver of proliferation requires both PgR and ER participation, meaning that PgR blockade reduces the ability of a cell to develop resistance to ER blockade – results that are consistent with ER-PgR synergy (Daniel *et al*, 2015).

3.5.2 In Vivo Experiments

Klijn and co-workers studied antiprogestin-antiestrogen interactions in rats bearing mammary tumors induced by dimethylbenzanthracene (DMBA). Two sets of experiments studied drug effects on tumor growth (proliferation) and/or tumor regression (tumor cell death; apoptosis) with: a) mifepristone and tamoxifen, administered alone and in combination; and b) the single and combination effects of the antiprogestin ORG 31.710 with tamoxifen. Treatment with mifepristone or tamoxifen, alone, inhibited tumor growth (90% and 75%, respectively), but did not lead to tumor remission. Combined treatment with mifepristone and tamoxifen resulted in additive tumor growth inhibitory effects, as well as a 50% remission in mammary tumor size. The researchers similarly reported that the antiprogestin ORG 31.710 in combination with tamoxifen was also effective in causing tumor regression - slightly more so (64%) than the combination of mifepristone and tamoxifen (50% regression). These experiments demonstrated that the combination of different antiprogestins with tamoxifen resulted in additive inhibitory effects on tumor cell growth and synergistic effects causing tumor regression (Bakker *et al*, 1989; reviewed in Klijn *et al*, 2000).

El Etreby *et al* (1998) reported the first in vivo study of the antitumor activity of an antiprogestin (mifepristone) and tamoxifen, alone and in combination, in xenograft models using MCF-7 human breast cancer cells implanted into “nude” mice. The studies documented

slow, estradiol-dependent tumor growth that was partially inhibited by treatment with tamoxifen, mifepristone, or estradiol withdrawal. In contrast, the combination of tamoxifen and mifepristone completely prevented or abolished tumor growth. The combination of tamoxifen and mifepristone was further observed to delay or prevent tumor escape (relapse) from the antiestrogenic (antitumor) effects of tamoxifen (El Etreby and Liang, 1998).

Nishino *et al* (1994) reported testing onapristone and the antiestrogen ICI 164384 (ICI) in a murine, MXT-mammary tumor model. Onapristone (5 mg/kg) administered for 3 weeks exerted an ovariectomy-like antitumor effect (56% inhibition), whereas ICI (30 mg/kg) was weakly effective (28% inhibition). The combination of onapristone and ICI was, however, distinctly more effective than the monotherapies or ovariectomy, causing 78% inhibition. A similar potentiation of antitumor effect by combined treatment with onapristone and ICI was shown in a DMBA-induced mammary tumor model in rat when onapristone (5 mg/kg) and ICI (30 mg/kg) were administered once daily sub cutaneously (s.c.) for 4 weeks. The remission rates of tumors found after treatment with ICI, onapristone, and the combination were 15%, 46%, and 71% respectively – a clear therapeutic improvement with the combination versus either drug, alone (Nishino *et al*, 1994).

Nishino *et al* (2009) studied the antitumor effects of combining tamoxifen with onapristone. In a study of rats bearing DMBA-induced tumors, treatment with onapristone or tamoxifen yielded complete remission in 10% and 20% of test animals, respectively. However, combined treatment with tamoxifen and onapristone yielded a synergistic effect with a 73% complete remission rate. A similar potentiation of the antitumor effect of tamoxifen and onapristone was observed in an NMU (N-nitroso-N-methylurea)-tumor model. Tamoxifen and onapristone, alone, yielded no complete remission, and partial remission rate of 30% on both drugs. In combination, tamoxifen and onapristone demonstrated remission rates of 20% complete and 80% partial. In these studies using NMU-induced mammary tumor models, treatment with the combination of tamoxifen and onapristone was much more effective than the corresponding monotherapies (Nishino *et al*, 2009).

Preclinical in vitro and in vivo studies spanning a period of 30 years provide consistent evidence that treatment with combination hormonal therapy (antiestrogen and antiprogestin) results in greater inhibition of tumor cell proliferation and enhanced cellular differentiation and apoptosis relative to treatment with either modality, alone. In addition, the combination of antiestrogen and antiprogestin therapy may delay or effectively inhibit the emergence of antiestrogen resistance. These studies further show that onapristone, per se, exhibits additive/synergistic effects with antiestrogens.

3.5.3 Summary and Conclusions

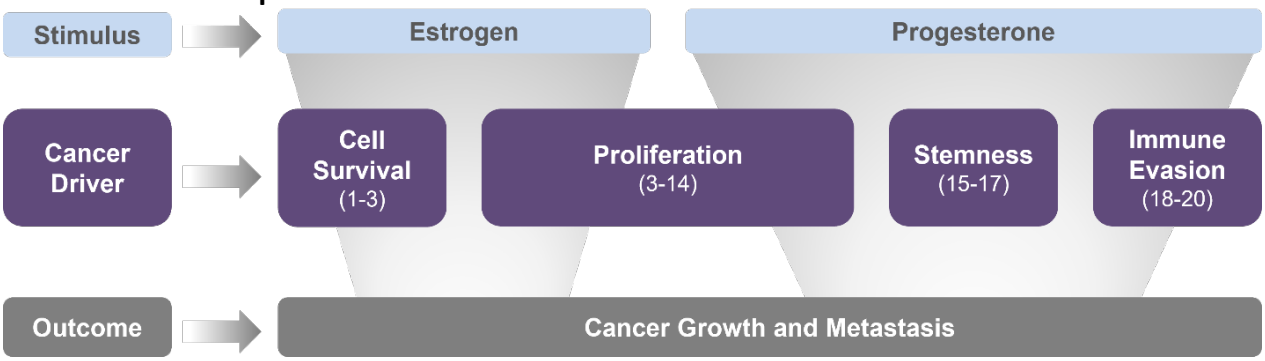
The in vitro and in vivo data summarized above demonstrate that combining ER plus PgR blockade increases tumor cell death and tumor regression to a greater extent than either intervention alone. This body of work necessarily points to additive or synergistic effects of ER/PgR blockade on tumor apoptosis.

A unifying view of why combined ER plus PgR blockade is more effective than either alone has

been suggested by Dr. Carol Lange (Professor of Medicine, University of Minnesota; personal communication). Dr. Lange's explanation is that ER blockade and PgR blockade additively or synergistically interfere with two different stages in the cell cycle; thereby driving cell differentiation and apoptosis to a greater degree than pharmacologically blocking the cell cycle at any one stage. This view is based on the fact that cancer, at its core, represents a dysregulation of cell cycle activities, including both proliferation and its key regulator - apoptosis. Blockade of any particular cell cycle stage, in a tumor or somatic cell results in the cell being forced into an alternate gene transcription program resulting in a change of cell phenotype or terminal differentiation associated with apoptosis (Pucci *et al*, 2000). For example, fulvestrant causes proteasomal degradation of ERα protein, shutting down estrogen signaling to induce proliferation arrest and apoptosis of estrogen-dependent breast cancer cells (Yeh *et al*, 2013). Phenotype shifts are seen both in the lab and in the clinic. For example, the SOLTI-1802 window of opportunity trial (NCT04142892), luminal-B patients treated with onapristone, showed a shift towards the luminal-A, more hormone-therapy sensitive status (Bellet *et al*, 2021). Looking at tumorigenesis from Dr. Lange's cell cycle perspective, ER and PgR signaling, while having overlapping transcriptional programs, drive two different stages in the cell cycle. ER signaling drives the S (synthesis) cell cycle stage, while PgR signaling promotes G0/G1 stages. In the S stage, cells continuously copy DNA and go on to divide. In contrast, PgR signaling promotes the G0/G1 stages, where G0 is a quiescent state in which cells have exited the cell cycle. Cells in a G0 state, such as cancer stem cells (CSCs), are notoriously difficult to attack, and can circulate in the bloodstream for many years before being triggered into an invasive/proliferative phenotype. The empirically observed effects of combined ER plus PgR blockade indicate that, when alternate metabolic pathways are unavailable, cells undergo apoptosis at a higher rate than with either therapy alone. It is not surprising that intervening at multiple stages of the cell cycle more effectively slows proliferation and enhances tumor regression than does intervening at just one stage. Joint ER/PgR blockade echoes the broad use of polypharmacy to achieve therapeutic synergies in medical practice.

ER and PgR are master transcription factors that, via autocrine and paracrine mechanisms, regulate many key cancer hallmarks in breast cancer including proliferation, cell survival, stemness and immune evasion, summarized in Figure 3. ER-PgR crosstalk is especially important in the co-regulation of tumor cell proliferation, suggesting that combined ER plus PgR blockade has the potential, in human, to more completely inhibit tumor cell proliferation while maximizing tumor apoptosis by interfering with multiple stages in the tumor cell replication cycle.

Figure 3: Hallmarks of Cancer Driven by Estrogen Receptor and Progesterone Receptor Activities



REFERENCES
1 Osborne et al, 2001
2 Stanculescu et al, 2010
3 Yu et al, 2012
4 Jensen et al, 2001
5 Platet et al 2004
6 Knutson et al, 2012, 2017
7 Tian et al, 2018
8 Beleut et al, 2010
9 Daniel and Lange, 2009
10 Michna et al, 1989
11 Lanari et al, 2012
12 Tanos et al, 2013
13 Giulianelli et al, 2012
14 Finlay-Schultz et al, 2015
15 Truong et al, 2019
16 Dwyer et al, 2020
17 Chen et al, 2020
18 Walter et al, 2017, 2020
19 Goodman et al, 2019
20 Sequeira et al, 2021

Three decades of research, summarized above, supports the core rationale for combining ER blockade (elacestrant) with PR blockade (onapristone), which is to evaluate the potential of the combination to control ER+/PgR+/HER2- breast cancer more effectively than either, alone.

4 OVERVIEW OF ONAPRISTONE

Onapristone is a type I antiprogestin which prevents the PgR from dimerizing (Allan *et al*, 1992) and blocks ligand-induced protein kinase-mediated phosphorylation of the PgR (Beck *et al*, 1996; Clemm *et al*, 2000; Knutson *et al*, 2017). Non-dimerized PgR does not bind to DNA (Graham *et al*, 2009). This aspect is key to the activity of onapristone, as dimerization is necessary for binding with progesterone receptor response elements (PRREs) in PgR-dependent genes and subsequently with co-activators to induce transcription. In addition, onapristone blocks coactivator binding to PgR 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 (Arnett-Mansfield *et al*, 2007). In contrast to mifepristone, onapristone reverses the assembly of DNA-bound PgR complexes induced by progestins (Rayasam *et al*, 2005).

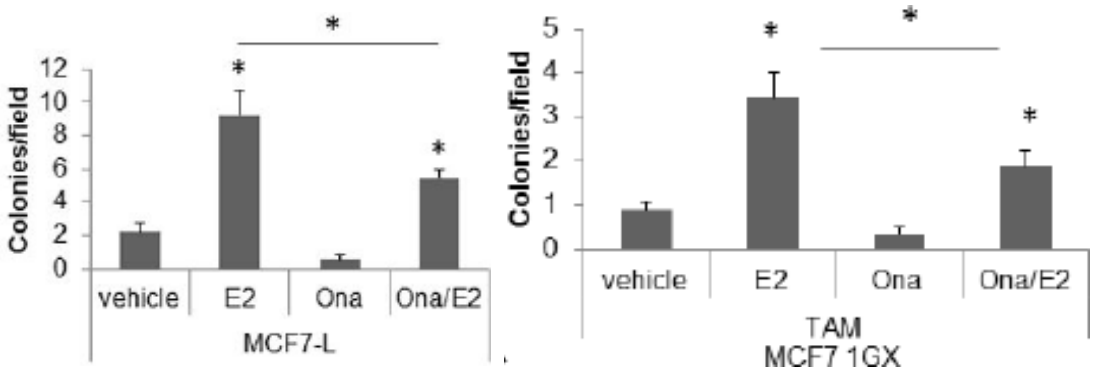
Onapristone treatment does not permit Ser294 phosphorylation, even in the presence of progesterone. This is in contrast to other anti-progestins (Beck *et al*, 1996; Afhüppe *et al*, 2009; Knutson *et al*, 2017). Knutson et. al. concluded that "Antiprogestins that block PgR SER294 phosphorylation should be included "up-front" as part of routine endocrine therapies for women undergoing long term management of ER+ luminal breast cancer," (Knutson *et al*, 2017).

4.1 Non-clinical experience

4.1.1 Onapristone Single Agent Activity

Onapristone also blocks estradiol-stimulated growth of soft agar colony formation of tamoxifen sensitive (MCF7L) and tamoxifen resistant (MCF7 1GX) cells (Figure 4; Daniel *et al*, 2015).

Figure 4: Onapristone blocks estradiol-stimulated growth



Source: Daniel *et al*, 2015

4.1.1.1 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 tamoxifen for 4 weeks. Monotherapy with either onapristone or tamoxifen caused partial remission of tumors in 30% of animals. When both anti-hormones were administered concomitantly, 80% partial and 20% complete remission was achieved, while ovariectomy induced 22% partial and 67% complete remission (Nishino *et al*, 2009).

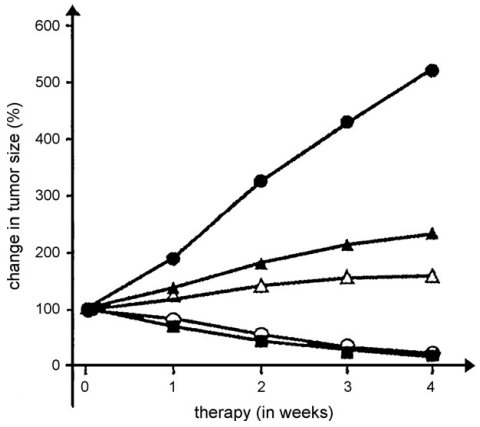
Table 2: Remission rates of NMU-induced mammary tumors in rats treated with onapristone, tamoxifen or a combination of both anti-hormones

	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 (Nishino *et al*, 2009).

Figure 5: Effect of onapristone and tamoxifen on the growth of NMU-induced mammary tumors in rats



Animals were treated SC once daily with onapristone (4 mg/kg) (Δ), tamoxifen (4 mg/kg) (▲) or a combination of both anti-hormones (■). Control animals (●) and ovariectomized animals (○) received only vehicle.
Source: Nishino 2009

Therefore, it is reasonable to hypothesize that the anti-tumor effect of tamoxifen may be enhanced by the combination with onapristone (Nishino *et al*, 2009; El Etreby *et al*, 1998).

4.1.2 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-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 (Additional information are provided in the onapristone investigators brochure).

Onapristone was highly protein bound in human female plasma with an unbound fraction of 0.56 ± 0.03%. Jang *et al* (1997) previously reported that onapristone does not bind to α-1-acid glycoprotein (Jang and Benet,1997).

Twelve (12) metabolites of onapristone were identified in rat, monkey and/or human liver microsomes (HLMs). In humans, 9 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 are appropriate toxicology test species. The chemical structure 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 HLMs.

Recombinant Cytochrome P (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 inhibited 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.

4.2 Safety, Pharmacology, and Toxicology of Onapristone

Safety pharmacology studies were conducted to identify the potential adverse effects of onapristone on several physiological systems (Table 3). 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 4 week repeat dose rat toxicology study. Cardiovascular safety pharmacology endpoints were evaluated in a GLP-compliant cynomolgus monkey study and HEK293 cells transfected with hERG.

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.

Table 3: 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 a 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
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 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 38bpm 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

Organ systems evaluated	Species/Strain	Method of admin.	Doses (mg/kg)	Gender and N per group	Noteworthy findings
					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 10mM (4.5 mg/mL) in the hERG test was observed; indicated the potential to prolong QT No effects were present at a concentration of 3mM (1.35 mg/mL)

Abbreviations: CNS = central nervous system; ECG = electrocardiography; FOB = functional operational batter; GLP = Good Laboratory Practices; hERG = human ether-a-go-go related gene

4.3 Clinical Experience

Onapristone (Ona) is a type I antiprogestin which prevents the PgR-A and PgR-B monomers from dimerizing, inhibits ligand-induced phosphorylation and prevents association of the PgR with its co-activators, thus preventing PgR-mediated DNA transcription (Klein-Hitpass *et al*, 1991). In contrast to other antiprogestins, Ona does not allow the PgR complex to bind to DNA, minimally modulates PgR-mediated genes, and inhibits ligand-induced PgR phosphorylation (Beck *et al*, 1996; Afhüppe *et al*, 2009). The clinical anticancer activity of Ona has been previously documented in patients with hormone therapy-naïve (Robertson *et al*, 1999) or tamoxifen-resistant (Jonat *et al*, 2002) breast cancer (BC).

More recently, an open-label, multicenter, randomized, parallel-group, phase 1 study (target n = 60; ClinicalTrials.gov identifier: NCT02052128) included female patients >18 years with PgR+ tumors. Fifty-two patients were randomized to five cohorts of extended release (XR) Ona 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 2 dose. Secondary endpoints included safety, clinical benefit, and pharmacokinetics (PK). 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 of Ona-XR was 50 mg BID. Median therapy duration was 8 weeks (range 2–44), and 9 patients had clinical benefit lasting at least 24 weeks (Cottu *et al,* 2018).

For 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 grade 3 elevation, eventually deemed due to disease progression in the liver). Refer to Section 4.2 for additional safety information. Additional safety information is presented in Table 4.

Table 4: Safety of Onapristone in Phase 1

Preferred Term	Overall (N = 52) n (%)	10 mg BID (N = 12[a]) n (%)	20 mg BID (N = 12[a]) n (%)	30 mg BID (N = 6) n (%)	40 mg BID (N = 10) n (%)	50 mg BID (N = 6) n (%)	100 mg BID (N = 6) n (%)
Any TEAE	**51 (98)**	**12 (100)**	**12 (100)**	**6 (100)**	**9 (90)**	**6 (100)**	**6 (100)**
Asthenia	27 (52)	6 (50)	6 (50)	4 (67)	5 (50)	3 (50)	3 (50)
GGT increase	18 (35)	5 (42)	3 (25)	2 (33)	5 (50)	2 (33)	1 (17)
AST increase	11 (21)	5 (42)	2 (17)	1 (17)	2 (20)	1 (17)	0
ALT increase	10 (19)	3 (25)	2 (17)	1 (17)	2 (20)	0	2 (33)
Nausea	9 (17)	3 (25)	1 (8)	2 (33)	1 (10)	1 (17)	1 (17)
ALP increase	8 (15)	3 (25)	1 (8)	2 (33)	2 (20)	0	0
Constipation	9 (17)	0	6 (50)	0	1 (10)	1 (17)	1 (17)
Abdominal pain	9 (17)	2 (17)	3 (25)	1 (17)	0	1 (17)	2 (33)
Vomiting	6 (12)	0	2 (17)	1 (17)	1 (10)	1 (17)	1 (17)
Pyrexia	9 (17)	0	3 (25)	2 (33)	2 (20)	0	2 (33)
Diarrhea	6 (12)	2 (17)	2 (17)	1 (17)	0	1 (17)	0
Peripheral edema	6 (12)	2 (17)	1 (8)	2 (33)	1 (10)	1 (17)	1 (17)
Hyperkalemia	6 (12)	2 (17)	1 (8)	0	1 (10)	1 (17)	1 (17)
Cough	6 (12)	0	1 (8)	2 (33)	0	1 (17)	1 (17)
Arthralgia	5 (10)	2 (17)	0	0	0	1 (17)	2 (33)

a 1 patient randomized to 20 mg was treated at 10 mg BID, and is included in all data tables as being at the 10 mg dose level.

Clinical benefit rate (partial response and stable disease lasting for at least 24 weeks) was observed in 17% of all patients including 1 partial response in a patient with ovarian cancer who had 3 prior therapies and 3 breast cancer patients with stable disease lasting for more than 24 weeks. These 3 breast cancer patients received 7, 7, and 3 therapies, respectively, prior to receiving Ona and two of these patients had liver metastases.

The authors concluded that onapristone-XR showed clinical benefit and a manageable safety profile in heavily pretreated patients with endometrial, ovarian and breast cancer (Cottu *et al*, 2018).

4.3.1 Pharmacokinetics of Onapristone

In the Phase 1 trial (Cottu *et al*, 2018), 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 C_{max} were dose-proportional across dose levels, with high correlation coefficients (R_2 values are 0.76 and 0.97, respectively, for Ona-XR (10mg-50mg BID) vs. immediate release 100mg QD (Figure 6 and Figure 7). Average T_{max} was 3.01 hours (2.71–3.2) vs 1.84 hours for extended release (XR) vs immediate release (IR) formulations, respectively, and concentrations of drug were sustained longer with a 60% (±20) relative bioavailability for XR vs IR formulation. Steady state for the XR formulation was attained before day 8, and the mean Ona minimum concentrations (C_{min}) at steady state were up to 5 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 $t_{1/2}$ for the XR 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 6: Onapristone $AUC_{0\text{-last}}$ versus first dose level

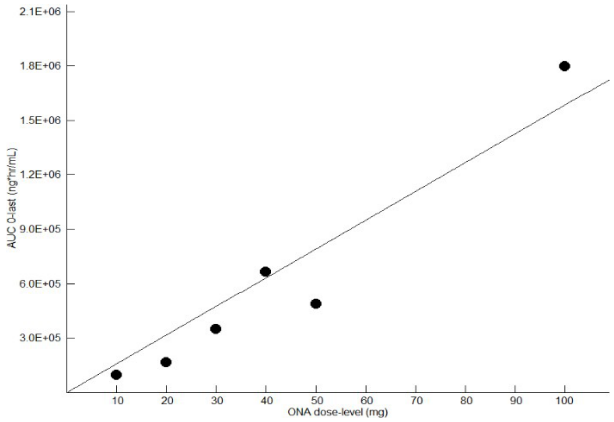
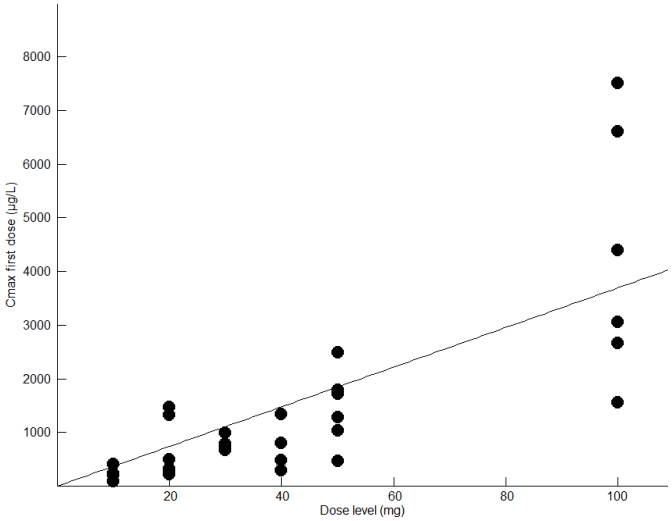


Figure 7: Onapristone C_{max} versus first dose level



5 OVERVIEW OF ELACESTRANT

Elacestrant is a tetrahydronaphthalene compound that acts as a selective estrogen receptor degrader (SERD) and is being developed for the treatment of estrogen receptor (ER) positive (+) advanced/metastatic breast cancer (mBC).

Patel *et al* (2019) evaluated elacestrant in multiple in vitro models and patient-derived xenografts that represent acquired and "de novo" CDK4/6i resistance. Elacestrant demonstrated growth inhibition in cells resistant to palbociclib, abemaciclib, and ribociclib in both estrogen receptor gene alpha (*ESR1)* wild-type and mutant backgrounds. The authors also reported that elacestrant downregulates several key cell cycle players and halts cell cycle progression in vitro and in vivo. The authors concluded that breast cancer tumor cells continue to rely on ER signaling to drive tumor growth despite exposure to CDK4/6i inhibitors. Importantly, elacestrant can inhibit this ER-dependent growth despite previously reported mechanisms of CDK4/6i resistance observed such as Rb loss, CDK6 overexpression, upregulated cyclin E1 and E2F1, among others (Patel *et al*, 2019).

Bardia *et al*, (2021) evaluated the safety and efficacy of elacestrant in a Phase 1 trial in heavily pretreated postmenopausal women with ER+, HER2- metastatic breast cancer, including those with *ESR1* mutation. Of 57 postmenopausal women enrolled, 50 received RP2D (345 mg once daily): median age, 63 years; median three prior anticancer therapies, including CDK4/6i (52%), SERD (52%), and *ESR1* mutation (circulating tumor DNA, 50%). No dose-limiting toxicities occurred; the most common AEs at RP2D (345-mg tablet; n=24) were nausea (33.3%) and increased blood triglycerides and decreased blood phosphorus (25.0% each). Most AEs were Grade 1-2 in severity. The objective response rate (ORR) was 19.4%, 15.0% in patients with prior SERD, 16.7% in patients with prior CDK4/6i, and 33.3% in patients with *ESR1* mutation. Elacestrant clinical benefit was associated with decline in *ESR1* mutant allele fraction (Bardia *et al*, 2021).

Oral administration of elacestrant had an absolute bioavailability of 10% and a mean half-life ranging from 39 to 47 h, reaching steady state after 5-6 days. Mean occupancy of the ER in the uterus after seven daily doses was 83% for 200 mg and 92% for 500 mg daily (Conlan *et al*., 2020).

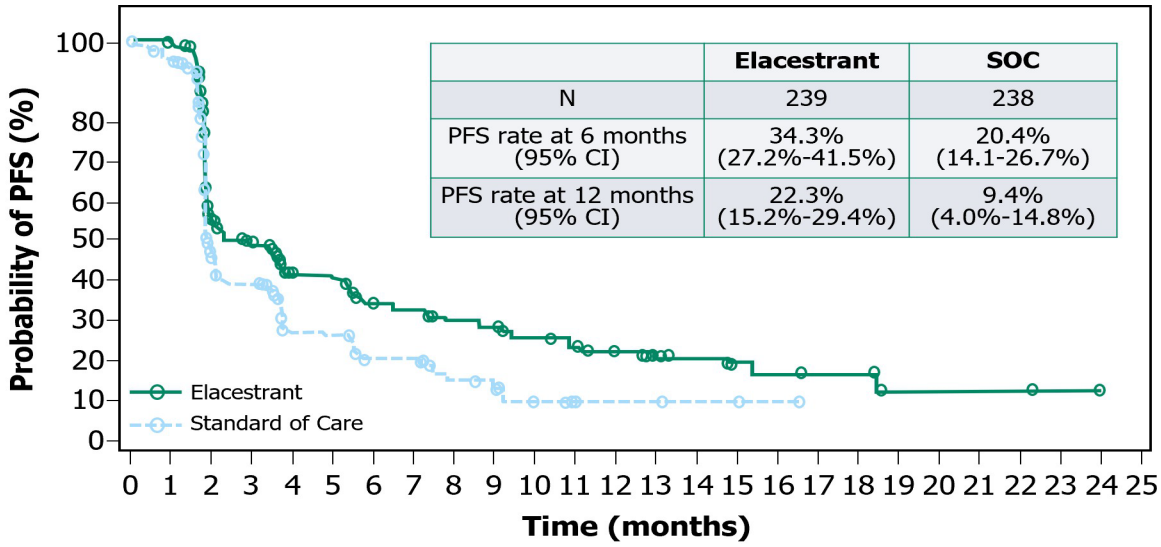
Bidard *et al* (2022) presented results from the EMERALD Phase 3 trial that compared elacestrant monotherapy at the dose of 345 mg QD (239 patients) to investigator's choice of endocrine monotherapy (standard of care [SoC]: fulvestrant, anastrozole, letrozole, or exemestane; 238 patients) in patients with ER+/HER2- advanced/metastatic breast cancer following CDK4/6i therapy. The trial had 2 primary endpoints: progression-free survival (PFS) in all patients and PFS in patients with tumors harboring *ESR1* mutations. Baseline patient and tumor characteristics were similar in both treatment arms.

In all patients, elacestrant was associated with a 30% reduction in hazard of progression or death, with a median PFS of 2.79 versus 1.91 months on elacestrant and standard of care, respectively (*P*=0.0018). The 6- and 12-months PFS estimates in all patients were 34.3% and 22.3%, respectively in the elacestrant arm and 20.4% and 9.4% in the SoC arm (Figure 8).

For patients with *ESR1* mutations, elacestrant was associated with a 45% reduction in hazard of progression or death, with a median PFS of 3.78 versus 1.87 months on elacestrant and standard of care, respectively (*P*=0.0005) Similarly, the 6- and 12-months PFS estimates were 40.8% and 26.8%, respectively in the elacestrant arm and 19.1% and 8.2% in the SoC arm. The PFS results were consistent in multiple pre-specified subpopulations (Figure 9).

The PFS results were consistent in multiple pre-specified subpopulations.

Figure 8: Progression-free survival of elacestrant and standard of care in all patients

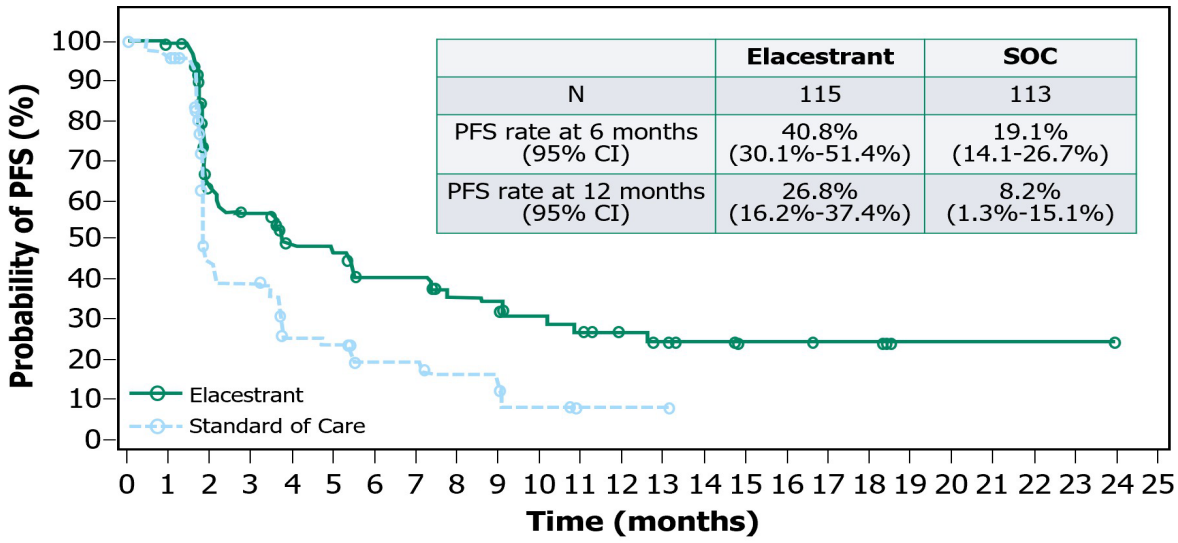


	Elacestrant	SOC
N	239	238
PFS rate at 6 months (95% CI)	34.3% (27.2%-41.5%)	20.4% (14.1-26.7%)
PFS rate at 12 months (95% CI)	22.3% (15.2%-29.4%)	9.4% (4.0%-14.8%)

Elacestrant	239	223	106	89	60	57	42	40	34	33	27	24	19	13	11	8	7	6	6	2	2	2	2	1	0
SOC	238	206	84	68	39	38	25	25	16	15	7	4	3	3	2	2	1	0							

Abbreviations: CI = confidence interval; PFS = progression-free survival; SOC = standard of care

Figure 9: Progression-free survival of elacestrant and standard of care in patients with *ESR1* mutations



	Elacestrant	SOC
N	115	113
PFS rate at 6 months (95% CI)	40.8% (30.1%-51.4%)	19.1% (14.1-26.7%)
PFS rate at 12 months (95% CI)	26.8% (16.2%-37.4%)	8.2% (1.3%-15.1%)

Elacestrant	115	105	54	46	35	33	26	26	21	20	16	14	11	9	7	5	5	4	4	1	1	1	1	1	0
SOC	113	99	39	34	19	18	12	12	9	9	4	1	1	1	0										

Abbreviations: CI = confidence interval; PFS = progression-free survival; SOC = standard of care

Elacestrant was well tolerated with manageable safety profile, consistent with other hormonal therapies. No fatal treatment-related AEs were reported in either of the two treatment arms and only 3 SAEs were considered related to elacestrant (Table 5) (Bidard *et al*, 2022).

Table 5: Elacestrant phase 3 EMERALD trial - Adverse events observed in 10% in either arm, irrespective of relationship to study drug

Adverse event	Elacestrant N=237		SoC N=229	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Nausea	83 (35.0)	6 (2.5)	43 (18.8)	2 (0.9)
Fatigue	45 (19.0)	2 (0.8)	43 (18.8)	2 (0.9)
Vomiting	45 (19.0)	2 (0.8)	19 (8.3)	0
Decreased appetite	35 (14.8)	2 (0.8)	21 (9.2)	1 (0.4)
Arthralgia	34 (14.3)	2 (0.8)	37 (16.2)	0
Diarrhea	33 (13.9)	0	23 (10.0)	1 (0.4)
Back pain	33 (13.9)	6 (2.5)	22 (9.6)	6 (2.5)
AST increase	31 (13.1)	4 (1.7)	28 (12.2)	2 (0.9)
Headache	29 (12.2)	4 (1.7)	26 (11.4)	0
Constipation	29 (12.2)	0	15 (6.6)	0
Hot flashes	27 (11.4)	0	19 (8.3)	0
Dyspepsia	24 (10.1)	0	6 (2.6)	0
ALT increase	22 (9.3)	5 (2.1)	23 (10.0)	1 (0.4)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; SoC = standard of care

The authors concluded that elacestrant has the potential to become a new treatment option in the studied patient population (Bardia *et al*, 2021).

6 OBJECTIVES AND ENDPOINTS

Objectives and endpoints for the Phase 1b and Phase 2 parts of the trial are provided in Table 6 and Table 7, respectively. Local radiological assessments will be used for all tumor assessment.

Table 6: Phase 1b – Objectives and Endpoints

	Objectives	Endpoints
Primary	Determine the recommended Phase 2 dose (RP2D) of this combination in patients with metastatic ER+, PgR+, HER-2- breast cancer.	Number of DLTs observed during the first cycle.
Secondary	Characterize the safety of elacestrant in combination with onapristone.	AEs and serious adverse events (SAEs) as well as changes in clinical laboratory values, vital sign measurements and ECG parameters.
	Evaluate the plasma PK of elacestrant as well as onapristone and their metabolites.	Standard plasma PK parameters including, but not limited to, the area under the plasma concentration-time curve over the dosing interval ($AUC_{0\text{-}tau}$), C_{max}, time of the maximum observed plasma concentration (T_{max}), and C_{trough}.
	Evaluate the efficacy of elacestrant in combination with onapristone, in terms of objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1, duration of response (DoR), clinical benefit rate (CBR), progression-free survival (PFS), and overall survival (OS). All efficacy analysis will be done for all patients and according to *ESR1* mutation status.	ORR: proportion of patients achieving a best overall response of confirmed partial or complete response (PR+CR) DoR: time from the date of the 1st documented CR/PR until 1st documentation of disease progression or death, whichever comes first. CBR: proportion of subjects achieving a best overall response of confirmed partial or complete response, or durable stable disease (duration is at least 23 weeks). PFS: time from the date of the 1st dose to the date of the 1st documentation of disease progression or death, whichever occurs 1st. OS: time from 1st dose date to the date of death from any cause.
Exploratory	Assess the pharmacodynamics (PD)	Changes in allele mutation frequencies in cell-free nucleic acid (cfNA) in blood.
	Evaluate relationship between efficacy and PD	Relationship between efficacy endpoints and allele mutation frequencies (at baseline and post baseline).
	Evaluate the efficacy of the combination according to *ESR1* mutation status	ORR, DoR, CBR, PFS, and OS

	Evaluate the efficacy of the combination according to the levels of the PgR	ORR, DoR, CBR, PFS, and OS

Table 7: Phase 2 – Objectives and Endpoints

	Objectives	**Endpoints**
Primary	Evaluate the efficacy of elacestrant in combination with onapristone, in terms of objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1. All efficacy analysis will be done for all patients and according to *ESR1* mutation status	ORR
Secondary	Evaluate the efficacy of elacestrant in combination with onapristone, in terms of DoR, CBR, PFS, and OS.	DoR, CBR, PFS, OS
	Further characterize the safety of elacestrant, in combination with onapristone at the RP2D	AEs and SAEs as well as changes in clinical laboratory values, vital sign measurements and ECG parameters
Exploratory	Assess the PD	Changes in biomarkers including, but not limited to, allele mutation frequencies in cfNA in blood
	Evaluate relationship between efficacy and PD	Relationship between efficacy endpoints and allele mutation frequencies (at baseline and post baseline)
	Evaluate the efficacy of the combination according to *ESR1* mutation status	ORR, DoR, CBR, PFS, and OS
	Evaluate the efficacy of the combination according to the levels of the PgR	ORR, DoR, CBR, PFS, and OS

7 POPULATION

The study will enroll up to 67 women and men with ER+, PR+, HER2- metastatic breast cancer who have progressed on or after prior antiestrogen plus CDK4/6 inhibitor combination therapy.

7.1 Inclusion Criteria

1. Women or men aged ≥18 years, at the time of informed consent signature. *Note:* Pre- and peri-menopausal women should receive goserelin for at least one month prior to initiating trial therapy, during the trial, and for at least one month after end of trial therapy. Men should receive triptorelin for at least one month prior to initiating trial therapy, during the trial and for at least one month after end of trial therapy.
2. Histopathologically or cytologically confirmed ER+, PgR+, HER2-, breast cancer, per local laboratory, as per the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines (Allison *et al*, 2020). *Note*: In the context of this trial, ER and PgR status will be considered positive if ≥10% of tumor cells demonstrate positive nuclear staining by immunohistochemistry.
3. At least one measurable lesion as per RECIST version 1.1. *Note*: Patients with stable brain or subdural metastases are allowed if the patient has completed local therapy and has discontinued the use of corticosteroids for at least 4 weeks before starting treatment in this study. Any signs (e.g., radiologic) or symptoms of brain metastases must be stable for at least 4 weeks before starting study treatment.
4. Prior therapy with an aromatase inhibitor or fulvestrant + a CDK4/6 inhibitor in the metastatic setting or in the adjuvant setting if within 12 months of last dose of adjuvant therapy. *Note:* Prior therapy with everolimus is allowed.
5. ECOG performance status of 0 or 1.
6. Patient has adequate bone marrow and organ function, as defined by the following laboratory values:
   a. Absolute neutrophil count ≥1.5 × 10^9/L
   b. Platelets ≥100 × 10^9/L
   c. Hemoglobin ≥9.0 g/dL
   d. Potassium, sodium, calcium (corrected for serum albumin) and magnesium CTCAE grade ≤1
   e. Cockcroft-Gault based creatinine clearance ≥50 mL/min.
      Note:
      Creatinine clearance (male) = ([140-age in years] × weight in kg)/ ([serum creatinine in mg/dL] × 72)
      Creatinine clearance (female) = (0.85 × [140-age in years] × weight in kg)/ ([serum creatinine in mg/dL] × 72)
   f. Serum albumin ≥3.0 g/dL (≥30 g/L)
   g. In absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3.0 × upper limit of normal (ULN). If the patient has liver metastases, ALT and AST ≤5 × ULN

h. Total serum bilirubin <1.5 × ULN except for patients with Gilbert's syndrome who may be included if the total serum bilirubin is ≤3.0 × ULN or direct bilirubin ≤1.5 × ULN.

7.2 Exclusion Criteria

1. Active or newly diagnosed CNS metastases, including meningeal carcinomatosis.
2. Breast cancer treatment-naïve patients in the metastatic setting.
3. Prior therapy with elacestrant, onapristone, or chemotherapy in the metastatic setting.
4. Patient has a concurrent malignancy or history of invasive malignancy within 3 years of enrollment, with the exception of basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix that has completed curative therapy.
5. Uncontrolled significant active infections.
   a. Patients with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infection must have undetectable viral load during screening.
   b. Patients known to be HIV+ are allowed as long as they have undetectable viral load at baseline.
6. Major surgery within 4 weeks before starting trial therapy.
7. Inability to take oral medication, or history of malabsorption syndrome or any other uncontrolled gastrointestinal condition.
8. Females of childbearing potential who:
   a. Within 28 days before study entry, did not use a highly effective method of contraception.
   b. Do not agree to use a highly effective method of contraception throughout the entire study period and for 28 days after trial therapy discontinuation.
9. Males who do not agree to abstain from donating sperm, or to use a highly effective method of contraception, during the course of the treatment period and for 28 days thereafter.
10. Known intolerance to either study drug or any of the excipients.
11. Patient is currently receiving or received any of the following medications prior to first dose of trial therapy:
    - Known strong or moderate inducers or inhibitors of cytochrome P450 (CYP) 3A4 within 14 days or 5 half-lives, whichever is shorter, (Refer to http://medicine.iupui.edu/clinpharm/ddis/),
    - Herbal preparations/medications within 7 days. These include, but are not limited to, St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.
    - Investigational anti-cancer therapy with 21 days or 5 half-lives, whichever is shorter.
    - Vaccination, including but not limited to vaccination against COVID-19, during the 7 days prior to randomization
12. Evidence of ongoing alcohol or drug abuse.

8 TRIAL THERAPY

8.1 Doses and Administration

All patients in Phase 1b and Phase 2 of this study will receive elacestrant and onapristone orally on a 28-day cycle. Patients should take elacestrant together with the first daily dose of onapristone at the same time in the morning every day. The second daily dose of onapristone should be taken approximately 12 hours after the morning dose. Both drugs should be taken with a glass of water with light food.

Elacestrant and onapristone tablets should be swallowed whole. Tablets should not be ingested if they are broken or cracked. Dosing should not be repeated if a patient vomits. If the elacestrant or onapristone dose was missed by more than 6 hours, it should be skipped, and the next dose should be taken at the usual time.

The starting doses in each of the Phase 1b cohorts are presented in Table 8.

Table 8: Starting dose of elacestrant and onapristone in Phase 1b

Cohort	Elacestrant dihydrochloride dose (QD)	Onapristone (BID)
Cohort 1	200 mg	40 mg
Cohort 2	300 mg	40 mg
Cohort 3	400 mg	40 mg
Cohort 4	400 mg	50 mg

All patients in the Phase 2 part of the trial will receive the recommended phase 2 dose selected from the phase 1b part in the trial.

8.2 Intra-patient Dose Escalation

Once a patient has completed Cycle 3 at the assigned dose level, intra-patient dose escalation will be allowed. Only patients who have not progressed on treatment and did not have a dose reduction because of adverse events, may escalate to the highest dose level that has completed DLT assessment and has been shown to be safe (no more than 1 DLT in 6 patients). Patients who follow the intra-patient dose escalation will not be included in the DLT analysis at the higher dose level.

8.3 Treatment Duration

Patients will continue to receive study treatment until any of the following occur:

- Disease progression
- Death
- Development of unacceptable toxicity considered related to study drug
- Patient request
- Withdrawal of consent
- Occurrence of pregnancy
- Investigator's decision

- Lost to follow-up
- Inability to comply with protocol requirements

The reason for treatment discontinuation will be documented. If a patient discontinues both study drugs, the patient will enter the Follow-Up Phase and complete protocol-specified off-treatment visits, procedures, and survival follow-up unless the patient withdraws consent.

The investigator should confirm whether a patient will discontinue trial therapy but agree to continue protocol-specified, off-treatment study visits, procedures, and survival follow-up, or whether the patient will withdraw consent. If a patient withdraws consent, the date will be documented in the source documents. In such a case, data collection for visits or assessments occurring after the date of consent withdrawal will not be allowed.

During the Follow-Up Phase, patients who have discontinued study treatment without progression will be followed for disease assessments every 8 weeks from the date of the last tumor assessment until radiological disease progression is documented or another anticancer therapy is initiated. Patients will be followed for AEs for 28 days after the last treatment administration or until resolution or stabilization of all treatment-related AEs to either ≤ Grade 2 or baseline, whichever is longer, or until the patient is lost to follow-up. At any time after 28 days from the last dose of study treatment, the Investigator may report any SAE that he/she believes is related to study treatment.

Patients who discontinue 1 of the 2 study drugs and continue therapy with the other one are considered *on treatment* until they discontinue the 2nd drug.

Average treatment duration is estimated to be 6 months. Patients who discontinue 1 of the 2 drugs and continue therapy with the other drug are considered 'on treatment' until they discontinue the second drug.

8.4 Study Drug Packaging and Labeling

The packaging and labelling of study will be performed under the responsibility of Context Therapeutics or its designee. The study drug will be packed in HDPE bottles (primary packaging). The HDPE bottles will be labelled in compliance with current valid international and national requirements.

8.5 Drug supply, storage, and Accountability

Context Therapeutics or its designee will provide both elacestrant and onapristone. Elacestrant dihydrochloride will be provided as coated tablets of 100 and 400 mg strength, which is equivalent to 86 and 345 mg of elacestrant free base respectively, to allow dose modification for management of AEs, in bottles of 30 tablets each. Onapristone-XR will be distributed by Context Therapeutics in 10 and 20 mg tablets in bottles of 60 tablets each.

Upon receipt of all study treatment, study site personnel or the designated pharmacist will open the shipment package, verify the contents as stated on the enclosed Delivery Note and confirm the receipt in the interactive response technology (IRT). The IRT will be used to record the study treatment delivery to study sites and patients, the inventory at the sites, including

dates, quantities, expire dates and batch/serial number.

The Investigator will be responsible for documenting the number and strength of tablets dispensed to the patient by entering the information in the source documents and in the eCRF to allow drug accountability.

Patients will be instructed to return used or unused IMP at each visit to allow drug accountability.

In addition, the sites will maintain drug accountability forms to document the dispensed and administered study treatment per patient.

The storage conditions for each drug will be described on the medication label. Medication labels will comply with the legal requirements in the US. The investigator should instruct the patient to take the study drugs as per protocol and drug accountability must be performed on a regular basis. Patients will be instructed to return unused study drugs to the site at the end of each cycle. The site personnel will ensure that the appropriate dose of each study drug is administered at each visit and will provide the patient with sufficient number of tablets for subsequent dosing.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the eCRF and pill diary. Throughout the study and at the end of the study, all remaining study treatment will be reconciled under the responsibility of the Investigator at the study site.

No later than the Site Close out Visit, the used (returned from patient) and unused study drug shall be returned to Context's designated depot. In case local destruction is required due to national legislation, a certificate of destruction, indicating the batch number and the box number, needs to be provided.

8.6 Dose Modification

Management of severe or intolerable adverse reactions may require temporary dose reduction and/or interruption of elacestrant and/or onapristone. Recommendations for dose reduction, interruption or discontinuation of either drug for the management of adverse reactions are summarized in Table 9 (hematologic toxicities) and Table 10 (non-hematologic toxicities). Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

The doses of 100 mg, 200 mg, 300 mg, and 400 mg of elacestrant dihydrochloride correspond to the doses of 86 mg, 173 mg, 258 mg, and 345 mg of elacestrant free base, respectively.

8.6.1 Hematologic Toxicities

Monitor complete blood cell (CBC) counts prior to the start of trial therapy, and at the beginning of each cycle, and as clinically indicated.

Table 9: Dose Modifications and Adverse Event Management Recommendation – Hematologic Toxicities

CTCAE Grade	Elacestrant Dihydrochloride	Onapristone
Grade 1 or 2	No dose adjustment is required	No dose adjustment is required
Grade 3 or 4	Withhold drug until recovery to Grade ≤2; resume at the same dose	Withhold drug until recovery to Grade ≤2; resume at the same dose
Febrile neutropenia (Grade 3 neutropenia with fever ≥38.5 °C and/or infection)	Withhold drug until recovery to Grade ≤2; resume at the same dose	Withhold drug until recovery to Grade ≤2; resume at the same dose

CTCAE = Common Terminology Criteria for Adverse Events.
Laboratory values that meet criteria listed in this table should be repeated and confirmed within 24 hours of the initial results being reported.

8.6.2 Nonhematologic Toxicities

Table 10: Dose Modifications and Adverse Events Management Recommendation – Nonhematologic Toxicities

CTCAE Grade	Elacestrant Dihydrochloride	Onapristone
Grade 1 or 2	No dose adjustment is required	No dose adjustment is required
Grade 3 or 4 (if persisting despite optimal medical care)	Withhold drug until symptoms resolve to Grade ≤2; Resume at the next lower dose	Withhold drug until symptoms resolve to Grade ≤2; Resume at the next lower dose

CTCAE = Common Terminology Criteria for Adverse Events

8.6.3 Strong or Moderate CYP3A Inducers or Inhibitors

Avoid concomitant use of strong or moderate inducers or inhibitors of CYP3A and consider an alternative concomitant medication with no or minimal CYP3A induction.

9 RISKS AND BENEFITS

9.1 Potential for Overlapping Toxicities

Based on the elacestrant available 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 latest version of elacestrant Investigator's Brochure.

9.2 Potential for Onapristone-Elacestrant Interactions

The design of the phase 1 part of the trial allows for detailed assessment of the impact of co-administration of both drugs on the PK of each one relative to known historical data about the PK of each drug when administered as monotherapy.

10 STUDY DESIGN AND ASSESSMENTS

This is a multicenter, phase 1b/2 trial. The phase 1b part of the trial is open label and aims to determine the RP2D of onapristone and elacestrant when administered together. The Phase 2 part of the trial will evaluate the efficacy and safety of this combination in patients with ER+/PgR+/HER2- advanced/metastatic breast cancer after prior therapy with a CDK4/6i.

10.1 Screening Assessments

The following information will be collected, and procedures will be performed for each patient at screening up to 21 days prior to Cycle 1 Day 1: signed ICF prior to any other study-related procedures, assessment of inclusion/exclusion criteria, medical history, physical examination, and collection of pretreatment whole blood sample for cfNA analysis

10.2 Tumor Assessments

Tumor assessments will be performed according to RECIST version 1.1. Investigator-determined response assessments will be performed at each assessment timepoint and entered onto the eCRF.

The following tumor assessments will be performed for all patients enrolled in both phases of the trial during Screening/Baseline period (Day -21 to Cycle 1 Day 1) and every 8 weeks (±7 days) after Cycle 1 Day 1, or as indicated if disease progression is suspected clinically) using the same imaging modality and under the same operating conditions as the Screening/Baseline scans.

- Chest: CT with contrast,
- Abdomen, pelvis, and other known or suspected sites of the disease: CT (with contrast) or MRI (with contrast)

If imaging with contrast is contraindicated or not available, imaging without contrast should be performed and reason for not using contrast should be captured in the source documents. For subjects with a history of protocol-eligible treated brain metastases, a brain scan will be required at all tumor assessment timepoints.

A bone scan using whole-body bone MRI, 99m-technetium-based bone scans, or 18F-sodium fluoride PET will be performed during Screening to establish a baseline (a bone scan performed per local SOC within 6 weeks before Cycle 1 Day 1 is acceptable), approximately every 24 weeks (in conjunction with a scheduled tumor assessment visit), and as clinically indicated. Lesions identified on bone scans should be followed with cross-sectional imaging.

All responses must be confirmed no less than 28 days following the initial assessment of response. In order for stable disease to be considered the best overall response, it must occur ≥6 weeks following the first dose of study drug.

Patients who discontinue study treatment without radiological disease progression will continue to have tumor assessments as per the Schedule of Assessments until radiological disease progression, death, or initiation of another anticancer therapy, whichever occurs first,

unless the study is terminated.

10.3 Pharmacokinetic Assessments

For all patients enrolled in the Phase 1b part of the trial, on Cycle 1, Day 15 blood samples to determine plasma concentrations of elacestrant, onapristone and their metabolites will be collected at pre-dose (within 1 hour before administration of study drug) and at the following time points (in hours) after dosing: 1 (±10 minutes), 2 (±20 minutes), 3 (±30 minutes), 6 (±30 minutes), 8 (±30 minutes), 12 (±90 minutes, before the second onapristone dose), and 24 hours (±60 minutes, must be before administration of the next day's dose of study drugs) post-dose.

10.4 Pharmacodynamic and Other Biomarkers Assessments

Whole blood samples for cell-free NA (cfNA) will be collected on Cycle 1 Day 1, Cycle 1 Day 15, every 8 weeks after Cycle 1 Day 1 in conjunction with radiological tumor assessment, and at the End of Treatment visit (the first visit on the day, or soon after the date of, treatment discontinuation for any reason). Whole blood samples will be collected from all subjects. Samples should be collected before dosing.

The cfNA isolated from blood plasma samples may be used to explore tumor genetic alterations, including mutations that may emerge with drug treatment. Samples may also be used for other biomarker discovery and/or validation to identify biomarkers that may be useful to predict treatment response outcomes.

Instructions for the processing, storage, and shipping of samples will be provided in the Laboratory Manual.

10.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all CTCAE v5.0 grades; regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; and performance of physical examinations.

The following will be monitored and recorded: physical examination, ECOG performance status, height, weight, and vital signs, 12-lead ECGs, ECHO or MUGA scan, and laboratory assessments.

10.5.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drugs are elacestrant and onapristone.

The criteria for identifying AEs are as follows:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. Note: Signs and symptoms should not be listed as a separate AE if the applicable diagnosis is being reported as an AE.
- Any new disease or exacerbation of an existing disease. However, disease progression should be captured under efficacy assessments rather than as an AE.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug.

All AEs, regardless of relationship to study drug or procedure, should be recorded starting from the time the subject signs the study ICF through 28 days after last treatment administration.

It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

Abnormal ECG results (QTcF prolongation) should be considered an AE if there is an increase of more than 60 milliseconds (ms) from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such. If sinus bradycardia is observed at EOT visit, follow-up ECGs should be performed weekly until heart rate has returned to at least 60 bpm.

All AEs must be followed for 28 days after the subject's last dose, or until resolution, whichever comes first. Subjects who discontinue 1 of the 2 drugs and continue therapy with the other one are considered on treatment until they discontinue the 2nd drug. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Subjects with onset of an AE or deterioration of a preexisting AE during the AE collection period will be followed until resolution to baseline, start of a new anticancer treatment, or death.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

10.5.1.1 Assessing Severity of Adverse Events

AEs will be graded on a 5-point scale according to CTCAE v5.0. Investigators will report CTCAE grades for all AEs (for both increasing and decreasing severity).

10.5.1.2 Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable

- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of non–study treatment-related factors that are known to be associated with the occurrence of the event

10.5.1.2.1 Classification of Causality

The relationship of each AE to each of the two study drugs, separately, will be recorded on the eCRF in response to the following two questions:

- Is there a reasonable possibility that elacestrant caused the AE?

Yes (related)	A causal relationship is a reasonable possibility.
No (not related)	A causal relationship is not a reasonable possibility.

And

- Is there a reasonable possibility that onapristone caused the AE?

Yes (related)	A causal relationship is a reasonable possibility.
No (not related)	A causal relationship is not a reasonable possibility.

10.5.1.3 Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (i.e., the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization of ≥24 hours or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no “adverse event” (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol

- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for collection of blood samples for PK assessment of study drugs
- Hospitalization for routine maintenance of a device (e.g., battery replacement) that was in place before study entry

10.5.1.4 Serious Adverse Event Reporting

10.5.1.4.1 Initial Reports

All SAEs occurring from the time of informed consent until 28 days following the EOT Visit must be reported to Worldwide Clinical Trials within 24 hours of the knowledge of the occurrence.

SAEs should be reported by entering the SAE information in the AE/SAE sections of the EDC system.

Questions relating to SAE reporting can be directed to Worldwide Clinical Trials at:
Fax: 886-387-5539
Email: drugsafety@worldwide.com

10.5.1.4.2 Follow-Up Reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of new information, the updated SAE information should be entered to EDC. Requested supporting documentation (e.g., patient discharge summary or autopsy reports) should be emailed to Worldwide Clinical Trials at the address above.

10.5.1.5 Expedited Reporting

Context Therapeutics/designee will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSAR) that are fatal or life-threatening as soon as possible to the Food and Drug Administration (FDA), and in any case no later than 7 days after knowledge by the Context Therapeutics/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the FDA as soon as possible but within a maximum of 15 days of first knowledge by the Context Therapeutics/designee.

The Context Therapeutics/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Context Therapeutics/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to investigational medicinal product.

10.5.2 Pregnancy Reporting

Female subjects with child-bearing potential who are likely to have children must undergo a serum pregnancy test before using the IMP. All female subjects with child-bearing potential and male subjects with female partners with child-bearing potential must take effective contraceptive measures after signing the ICF until 30 days after the last dose of IMP.

Pregnancy:

During the study treatment period, female subjects should stop IMP as soon as being found pregnant. If a female subject or a female partner of a male subject become pregnant during the study treatment period until 6 months after the last dose of IMP, the investigator should be notified immediately. The investigator should complete the "Pregnancy Report Form" and report it to Context Therapeutics/designee within 24 hours of being notified. The investigator should follow the pregnancy to determine the outcome of the pregnancy, and report accordingly to the above method within 24 hours after obtaining the pregnancy outcome.

Congenital Anomalies/Birth Defects:

Any congenital anomaly/birth defect in a child born to a female subject exposed to study drug or the female partner of a male subject exposed to study drug should be classified as a SAE, recorded on the Adverse Event eCRF, and reported to Context Therapeutics/designee immediately (i.e., no more than 24 hours after learning of the event).

Reporting: For the aforementioned pregnancy outcome that meets the SAE criteria, in addition to the “Pregnancy Report Form”, the investigator should fill in the “Serious Adverse Event Report Form” and report it to Context Therapeutics/designee immediately (i.e., no more than 24 hours after learning of the event) via EDC.

10.5.3 Laboratory Measurements

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 11. The Schedule of Procedures/Assessments (Table 12) shows the visits and timepoints at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 11: Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, platelets plus reticulocyte counts, RBC count, and total WBC count with 5-part differential
Coagulation	INR, PT, aPTT
Comprehensive metabolic panel	BUN, creatinine, eGFR, sodium, calcium (corrected for serum albumin), potassium, chloride, phosphate, and magnesium, carbon dioxide, fasting glucose, fasting amylase, fasting lipase, albumin, total protein, total and direct bilirubin, ALP, AST, ALT, GGT, LDH, and thyroid function tests (TSH and Free T4)

Category	Parameters
Virology	HBV, HCV
Urine dipstick	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; GGT = gamma-glutamyl transpeptidase; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = International normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; RBC = red blood cell; T_4 = thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cell.

All hematology, blood chemistry (including pregnancy test, as applicable), and urinalysis samples are to be obtained prior to study drug administration, and results will be reviewed prior to administration/dispensing of study drug at the beginning of each treatment cycle.

For all safety assessments, the sites will use local laboratories. Central laboratory will be used for PK and PD assessments.

10.5.4 Vital Signs and Weight Measurements

Vital sign measurements (i.e., resting heart rate, BP, respiratory rate, oral temperature) and weight (kg) will be obtained at the visits designated in the Schedule of Procedures/Assessments (Table 12) by a standard method. Blood pressure and pulse will be measured after the subject has been resting for 10 minutes. All BP measurements should be performed on the same arm, preferably by the same person. For subjects with an elevated BP (≥140/90 mmHg), confirmation should be obtained by performing 3 measurements (at least 5 minutes apart) to yield a mean value. Systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg should be confirmed by repeat measurements after 1 hour.

10.5.5 Physical Examinations

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 12). Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the AEs eCRF.

10.5.6 Electrocardiograms

ECG assessments will be performed throughout the study at Screening/Baseline, Day 1 of each cycle, EoT visit, and Safety Follow-up visit.

Triplicate 12-lead ECG will be performed pre-dose after the patient has been resting for 10 minutes. The ECGs should be taken while the patient is in a semi-recumbent position. Triplicate ECGs should be taken approximately 2 minutes apart. Values from each of the triplicate ECGs will be captured in the eCRF (heart rate, QTcF, and QTcB).

An additional ECG will be performed at the Tmax of each drug (3 hours ± 30 minutes, for both elacetrant and onapristone) for all patients enrolled in the Phase 1b part of the trial at Cycle 1,

Day 15 just before the PK sample scheduled for this timepoint.

In addition, if clinically indicated, additional ECGs and/or cardiac enzyme evaluations should be performed.

10.5.7 Other Safety Assessments

A MUGA scan or an ECHO to assess left ventricular ejection fraction (LVEF) will be performed at screening and if clinically indicated thereafter. MUGA scans and ECHO should be performed locally in accordance with the institution's standard practice. LVEFs as assessed by the institution will be entered onto the eCRF. Investigator assessment will be based upon institutional reports.

10.5.8 Pregnancy Test

A serum pregnancy test must be performed at Screening for all women of childbearing potential (i.e., pre- and perimenopausal subjects). There is no need to repeat the test on Cycle 1 Day 1 if performed within 72 hours. Thereafter, during the study, serum or urine testing should be performed at D1 of each cycle. A serum testing should be performed to confirm a positive urine testing.

10.5.9 Remote Visits

For patients who experience significant hardship coming to the study center, remote visits (Telehealth and Home care visits), if allowed by local law, may be performed after sponsor approval instead of visits designated to be conducted at the research site. During these remote visits, the Health Care Provider will assess patient safety and collect relevant data, including but not limited to, drug compliance, luteinizing hormone-releasing hormone (LHRH) compliance as applicable, compliance with contraception use as indicated, new AEs or SAEs, new concomitant medications, review of laboratory and tumor assessments.

Table 12: Schedule of Assessments

Period	Screening	Cycle 1			Cycle 2		Cycle 3+	EOT	Safety Follow-up[a]	Survival[b, c] Follow-up
Study Day / Procedure	D-21 to D1	D1 (±1)	D8 (±1)	D15 (±2)	D1 (±3)	D15 (±3)	D1 (±3)		28 days (+7)	
Informed consent	X									
Eligibility criteria	X									
Medical history	X									
Concomitant medications	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	
Physical examination[d]	X	X	X	X	X	X	X	X	X	
ECOG performance status	X	X			X		X	X	X	
Triplicate 12-lead ECG[e]	X	X		X	X		X	X	X	
Pregnancy test[f]	X				X		X	X		
CBC[g]	X	X	X	X	X	X	X	X	X	
CMP[h]	X	X		X	X	X	X	X	X	
Coagulation	X				X		X	X	X	
HBV, HCV[i]	X									
Urine testing dipstick[j]	X				X		X	X	X	
Study treatments dispensing/return/ accountability[k]		X	X	X	X	X	X	X		
PK samples[l]				X						
PD samples (cfNA whole blood)[m]		X		X			X	X		
PET scan or whole-body bone scan[n]	X									
CT/MRI scans[o]	X						X	X		
Brain CT or MRI[p]	X									
Survival follow-up[a]										X

CBC = complete blood cell (count), cfNA = circulating free nucleic acid, CMP = comprehensive metabolic panel, eCRF = electronic case report form, CRP = C-reactive protein, CT = computed tomography, D = day, ECG = electrocardiogram, ECHO = echocardiogram, ECOG = Eastern Cooperative Oncology Group, EOT = end of treatment, HBV = hepatitis B virus, HCV = hepatitis C virus, INR = international normalized ratio, IV = intravenous, MRI = magnetic resonance imaging, PET = positron emission tomography, PK = pharmacokinetics, QTcF = QT interval corrected for heart rate using Fridericia's formula, T_4 = thyroxine, TSH = thyroid-stimulating hormone.

Protocol assessments, including labs, performed within 3 days prior to D1 of the next cycle (including cycle 1) do not need to be repeated on Day 1 of the new cycle.

a. All patients will be followed for AEs for 28 days after the last treatment administration or until resolution or stabilization of all treatment-related AEs to either ≤ Grade 2 or baseline, whichever is longer, or until the patient is lost to follow-up. At any time after 28 days from the last dose of study treatment, the Investigator may report any SAE that he/she believes is related to study treatment. Patients who discontinue 1 of the 2 oral drugs and continue therapy with the other drug are considered on treatment until they discontinue the second drug.

b. All patients will be followed for survival approximately every 3 months for up to 24 months after enrollment of the last patient. Survival follow-up may be done by telephone call at the investigator's discretion. Additional survival data may be requested prior to interim or main analyses.

c. The following information will be collected for the first anticancer systemic therapy used after discontinuation of trial therapy: Regimen individual treatments, start date, end date, and best overall response.

d. Physical examinations will include measurements of weight and vital signs (resting heart rate, blood pressure, respiratory rate, oral temperature). No need to repeat physical examinations on Cycle 1 Day 1 if the baseline physical examination was performed ≤3 days. Height will be recorded at the screening visit only. Scheduled vital signs, and laboratory tests should be performed predose.

e. At all indicated visits, standard 12-lead ECG will be performed in triplicate predose after the patient has been resting for 10 minutes and should be taken approximately 2 minutes apart while the patient is in a semi-recumbent position. An additional ECG will be performed at the T_{max} of each drug (3 hours ± 30 minutes, for both elacestrant and onapristone) for all patients enrolled in the Phase 1b part of the trial at Cycle 1, Day 15 just before the PK sample scheduled for this timepoint.

f. Only required for pre- and perimenopausal women. Pregnancy test during the screening period should be serum (no need to repeat on Cycle 1 Day 1 if within 72 hours). During the study, urine or serum testing should be performed at Day 1 of each cycle. If a urine test was positive, serum testing should be performed for confirmation.

g. CBC count consisting of red blood cell count (RBC), hematocrit, hemoglobin, mean corpuscular volume (MCV), mean corpuscular hemoglobin, total white blood count (WBC) with 5-part differential, and platelet count plus reticulocyte count. CBCs are collected every visit before treatment.

h. Comprehensive metabolic panel (CMP) includes blood urea nitrogen (BUN), creatinine, glomerular filtration (eGFR), sodium, calcium (corrected for serum albumin), potassium, chloride, phosphate, and magnesium, carbon dioxide, fasting glucose, fasting amylase, fasting lipase, albumin, total protein, total and direct bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase, and thyroid function tests (TSH and Free T4).

i. See Appendix 1 for HBV and HCV testing criteria.

j. If abnormalities are present, microscopic testing should be done.

k. Elacestrant and onapristone: starting Cycle 1 Day 1. One cycle is 4 weeks (28 days). Trial therapy should be dispensed, and patient's drug administration diary (pill diary) should be reviewed at the beginning of each cycle.

l. For phase 1b patients only: on Cycle 1 Day 15 blood samples to determine plasma concentrations of elacestrant, onapristone and their metabolites will be collected at pre-dose (within 1 hour before administration of study drug) and 1 (±10 minutes), 2 (±20 minutes), 3 (±30 minutes), 6 (±30 minutes), 8 (±30 minutes), 12 (±90 minutes, before the second onapristone dose), and 24 hours (±60 minutes, must be before administration of the next day's dose of study drugs) post-dose.

m. Whole blood for cfNA will be collected on Cycle 1 Day 1, Cycle 1 Day 15, every 8 weeks after Cycle 1 Day 1 in conjunction with radiological tumor assessment, and at the End of Treatment visit (the first visit on the day, or soon after the date of, treatment discontinuation for any reason). Samples should be collected before dosing.

n. A bone scan using whole-body bone MRI, ^{99}m-technetium-based bone scans, or ^{18}F-sodium fluoride PET will be performed during Screening to establish a baseline (a bone scan performed per local SOC within 6 weeks before Cycle 1 Day 1 is acceptable), approximately every 24 weeks (in conjunction with a scheduled tumor assessment visit), and as clinically indicated. Lesions identified on bone scans should be followed with cross-sectional imaging.

o. Tumor assessments will be performed at baseline and every 8 weeks after Cycle 1 Day 1 until radiological disease progression and will include:

- Chest: CT with contrast,
- Abdomen, pelvis, and other known or suspected sites of the of disease: CT (with contrast) or MRI (with contrast)

If imaging with contrast is contraindicated or contrast is not available, imaging without contrast should be performed and reason for not using contrast should be captured in the source documents. Tumor assessments will be performed using the same imaging modality and under the same operating conditions as the baseline scans.

p. Brain CT with contrast or MRI (pre- and post-contrast): at baseline and if clinically indicated during the study.

If imaging with contrast is contraindicated or contrast is not available, imaging without contrast should be performed and reason for not using contrast should be captured in the source documents.

11 REGULATORY AND ETHICAL COMPLIANCE

11.1 Responsibilities of The Investigator and IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board (IRB) / Independent Ethics Committee (IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Context Therapeutics before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Context Therapeutics monitors, auditors, Context Therapeutics Clinical Quality Assurance representatives, designated agents of Context Therapeutics, IRBs/IECs and regulatory authorities as required.

Documented study approval from the IRB/IEC chairman must be sent to the principal investigator (PI) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required. Where appropriate, at the end of the study, the sponsor should notify the IRB/IEC and Competent Authority (CA) within 90 days.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC within institutional time requirements, and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

The definition of the end of the study is approximately six months after the cutoff date for the final analysis.

11.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 (R2) Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Pharmaceuticals

for Human Use

- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

11.3 Informed Consent

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Context Therapeutics will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed informed consent form suggested by the investigator must be agreed to by Context Therapeutics before submission to the IRB/IEC, and a copy of the approved version must be provided to the Context Therapeutics monitor after IRB/IEC approval.

11.4 Amendments to the Protocol

Any change to the protocol can only be made in a written protocol amendment that must be approved by Context Therapeutics, Health Authorities where required, and the IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Context Therapeutics should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days.

11.5 Discontinuation of the Study

Context Therapeutics reserves the right to discontinue this study under the conditions specified in the clinical trial agreement.

12 STATISTICAL METHODS

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked. Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock.

12.1 Definitions of Analysis Sets

- Safety Analysis Set: which will consist of all subjects who receive at least 1 dose of study drugs (either elacestrant, onapristone, or both). This will be the analysis set for all safety evaluations except DLT results in the phase 1b part of the trial.
- Dose-Limiting Toxicity (DLT) Evaluable Set: which will consist of all subjects who were evaluable for DLT assessment in Phase 1b part of the study. This will be the analysis set for DLT results.
- Full Analysis Set (FAS): which will consist of all subjects who receive at least 1 dose of study drug. This will be the basis for PFS and OS analysis.
- Response-Evaluable Set (RES): which will consist of those subjects who receive at least 1 dose of study drug and have measurable disease at baseline and at least 1 postbaseline tumor assessment. This will be the primary analysis set for response and clinical benefit assessment.
- Subset analysis for $ER\alpha^{mut}$ and $ER\alpha^{WT}$: which will consist of all subjects who receive at least 1 dose of study drug and are either $ER\alpha^{mut}$ or $ER\alpha^{WT}$.
- Pharmacokinetic Analysis Set: which will consist of subjects who received at least 1 dose of study drug and have valid plasma concentrations (at least 3 valid concentrations for noncompartmental analysis).
- Pharmacodynamics Analysis Set: which will include all subjects who receive at least 1 dose of study drug and have evaluable PD data (baseline and at least once after starting trial therapy).

12.2 Data Analysis

Descriptive statistics, including mean, median, standard deviations and ranges for all continuous measures will be tabulated and reported. Percentages and frequencies for all categorical measures will also be presented. Time-to-event endpoints will be reported using Kaplan-Meier estimates. Baseline demographics and other characteristics will be reported.

In general, statistical analyses will be performed for the overall population and subgroups of population. Detailed presentation plan and definition of subgroups will be included in the SAP.

12.3 Subject Disposition

The number of subjects screened for participation and number enrolled overall and by study part will be tabulated along with the proportion included in each analysis population. The proportion of subjects who discontinue study treatment will be tabulated, along with the primary reason for discontinuation.

12.4 Demographic and Other Baseline Characteristics

Demographic and baseline disease characteristic data will be summarized descriptively. Data to be tabulated will include at least demographic features such as sex, age, and race, as well as weight and disease-specific status and medical history.

12.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the current version of the World Health Organization Drug Dictionary (WHO DD).

The number (percentage) of subjects who took prior and concomitant medications will be summarized on the FAS by study part, cohort and overall Anatomical Therapeutic Chemical (ATC) class (i.e., anatomical class, therapeutic class, pharmacologic class, chemical class), as well as WHO DD preferred term (PT).

- Prior medications will be defined as medications that stopped before the first dose of study drug.
- Concomitant medications will be defined as medications that started after the date of the first dose of study drug up to 28 days after the subject's last dose.

All medications will be presented in subject data listings.

12.6 Sample size

12.6.1 Phase 1b

The Phase 1b aims at selecting the RP2D dose, defined as a dose that is associated with less than 33% of patients experiencing a DLT, that is, ≤1 patient experiencing a DLT out of 6 DLT-evaluable patients.

Patients who receive <70% of the scheduled therapy during Cycle 1 of either drug, for reasons other than toxicity, will not be considered evaluable for DLT assessment and will be replaced. Disease progression and AEs deemed related to disease progression will not be considered DLTs.

The Phase 1b will have between 6 and 24 DLT-evaluable patients.

12.6.2 Phase 2

A Simon two-stage design (Simon, 1989) will be used to evaluate the ORR in the Response-Evaluable Set (RES). The null hypothesis that the true RR in the RES is 5% will be tested against a one-sided alternative of 20%.

Among the first 21 response-evaluable patients, if there is no or only one confirmed response, enrollment will be stopped. This futility analysis will be performed approximately 16 weeks after enrollment of the 21st patient. If there are 2 or more objective responses in these 21 patients, additional patients will be accrued in order to have a total of 41 response-evaluable patients. Patients treated at the RP2D in the Phase 1b part of the trial will be counted as part of the Phase 2 patients.

While accumulating data from stage 1, enrollment into stage 2 may be continued or held depending on agreement between the SSC and the Sponsor.

By the end of the study, if there are 5 or more objective responses in 41 response-evaluable patients, the null hypothesis will be rejected, and the treatment evaluated in this arm will be considered active in this patient population. This design yields a type I error of 0.05 (one-sided) and power of 90% with the true RR of 20%.

Patients who are not deemed response-evaluable will be replaced. It is anticipated that this category will not exceed 10%, that is, approximately 4 additional patients.

The total number of phase 1 and phase 2 patients will be approximately 67. It is estimated that approximately 40% of all patients will have tumors harboring *ESR1* mutations. After enrolling approximately 40 patients, a review of *ESR1* mutation status will be performed and enrollment may be restricted to patients with *ESR1* mutations in order to allow for meaningful assessment of efficacy in this group of patients.

12.7 Extent of Exposure

Descriptive statistics for subjects treated, including the duration of treatment, the number of cycles received, and the number of subjects requiring dose changes (interruption and/or reduction), will be presented. A by-subject listing of the date of study drug administration and the dose administered will be presented.

12.8 Efficacy Analysis

The final efficacy analyses will be based on data collected as of the data cutoff date, i.e., when the last subject on trial therapy has completed at least 6 cycles of treatment, that is, 24 weeks.

ORR and CBR will be calculated with exact 95% confidence intervals using the method of Clopper and Pearson.

DoR will be calculated for subjects achieving a best overall response of confirmed CR or confirmed PR.

For DoR, PFS, and OS, medians will be calculated using Kaplan-Meier estimates. DoR, PFS, and OS will be reported in both summary tables and plotted with Kaplan-Meier curve.

12.9 Safety Analysis

12.9.1 Analysis of adverse events

The determination of the MTD and/or RP2D will be based on DLT Evaluable Set. Subjects not

evaluable for DLT assessment will be replaced. In the DLT Evaluable Set, the number (percentage) of subjects with DLTs will be presented by dose level cohort for Phase 1b of the study. A listing of subjects with DLTs will be provided.

A treatment-emergent adverse events (TEAEs) is defined as an AE that:

- emerges during treatment, having been absent at pretreatment (Baseline),
- reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- worsens in severity during treatment relative to the pretreatment state when the AE is continuous.

Only those AEs that are treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The AEs will be coded using MedDRA and summarized using SOC and PT. AEs will be coded to the MedDRA (Version 22.1 or higher) lower-level term closest to the verbatim term. The linked MedDRA PT and primary SOC are also captured in the database. Summaries of SAEs, AEs leading to treatment discontinuation, AEs by maximum NCI CTCAE v5.0 grade, and AEs related to study treatment will also be presented by dose level. AEs will be collected for each subject until 28 days after last trial therapy administration.

All safety analyses will be performed on the Safety Analysis Set. Safety data will be summarized on an “as treated” basis using descriptive statistics (e.g., n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include TEAEs, clinical laboratory parameters, vital signs, and 12-lead ECG results. The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drugs.

Safety will be assessed through the analysis of the reported incidence of TEAEs, which will be graded according to NCI CTCAE v5.0. The TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA,), and summarized using system organ class (SOC) and PT by treatment group/dose level for all subjects in the Safety Population. In addition, summaries of SAEs, AEs leading to treatment discontinuation, AEs by maximum grade, and AEs related to study treatment will also be presented by dose level.

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

Other safety endpoints, including laboratory results, vital signs, and ECG findings, will be summarized for all subjects in the Safety Analysis Set.

Concomitant medications will be coded using the WHO DD and they will be listed and summarized by dose level.

Evaluation of safety will be performed on the Safety Analysis Set except for the determination of the MTD during Phase 1 (dose escalation). The determination of the MTD will be based on all DLT-evaluable subjects enrolled in the Phase 1b of the study.

Subjects who do not receive study drug for at least 70% of the planned dose of either drug during the first cycle (28 calendar days) for reasons other than AEs, e.g., non-compliance, will be replaced. The subjects who are replaced will not be considered evaluable for DLT assessments.

Safety data to be evaluated include AEs, clinical laboratory results, vital sign measurements, and ECG parameters (hear rate, QTcF, QTcB) will be evaluated.

Safety parameters will be summarized using descriptive statistics (mean, standard deviation, median, Q1, Q3, and range for continuous variables; numbers and percentages for categorical measures).

12.9.2 Analysis of laboratory values

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters, the actual value and the change from baseline to each postbaseline visit will be summarized by visit using descriptive statistics. Qualitative parameters will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit will be reported using shift tables. Percentages will be based on the number of subjects with both non-missing baseline and relevant postbaseline results.

Furthermore, the frequency of laboratory abnormalities by maximum post-baseline CTCAE grade will be tabulated for selected laboratory parameters. Shift tables will also be produced for these parameters based on the baseline CTCAE grade and the maximum CTCAE grade post baseline. Details will be provided in the SAP.

12.9.3 Vital Signs and body weight

Changes in vital sign parameters and body weight will be summarized over time, and any abnormal values will be tabulated.

Descriptive statistics for vital signs parameters (i.e., systolic and diastolic BP, pulse, respiratory rate, temperature, and weight) and changes from baseline will be presented by visit.

12.9.4 Electrocardiograms

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group. Summary tables and listings and changes from baseline will be presented.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTcF during the treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTcF interval prolongation:

- QTcF interval >480 ms
- QTcF interval >500 ms

Change from baseline in QTcF interval:

- QTcF interval increases from baseline >30 ms
- QTcF interval increases from baseline >60 ms
- QTcF interval >500 ms or QTcF interval increases from baseline >60 ms

All ECG abnormalities will be listed on a per-subject basis.

12.10 Pharmacokinetics and Pharmacodynamics Analyses

12.10.1 Pharmacokinetic Analyses

The plasma concentrations of elacestrant and onapristone and, if needed, their metabolites will be presented by dose level, as the number of subjects with data, geometric mean, mean, standard deviation (SD), median, minimum, and maximum values by nominal sampling timepoint. The PK parameters will include, as applicable, C_{max} (time of the maximum observed plasma concentration [T_{max}]), $AUC_{0\text{-}24}$ (AUC from zero time to 24 hours), $AUC_{0\text{-}t}$ (AUC from zero time to last measurable concentration), $AUC_{0\text{-}inf}$ (AUC from zero time to infinity), percentage of AUC that is due to extrapolation from the last measurable concentration to infinity ($\%AUC_{Extrap}$), apparent terminal disposition rate constant (λ_z), apparent plasma terminal elimination half-life ($t_{½,z}$), apparent total plasma clearance (CL/F), and apparent volume of distribution (V/F) and will be summarized by cohorts and day, with the number of measurements, number of non-missing data, the number of subjects, geometric mean (CV%), mean, SD, median, minimum, and maximum.

The DDI effect for elacestrant and onapristone will be assessed relative to historical monotherapy data for elacestrant and onapristone.

12.10.2 Pharmacodynamics Analyses

The whole blood samples will be analyzed for evaluation of cfNA as a source of circulating biomarker (NA mutations). The samples might be used for exploratory analysis for evaluation of response-related outcomes, as well as for potential use in companion diagnostic and drug development.

Exposure-response with biomarkers and/or other efficacy endpoints will be explored as appropriate with a population PK model-predicted exposure values.

12.11 Interim Analysis

No formal interim analyses are planned. However, the cumulated safety and efficacy data by dose level cohort will be reviewed periodically by the sponsors and investigators. The continuation of study enrollment will depend on the totality of the efficacy and safety data.

13 REFERENCES

Adams S, Gatti-Mays ME, Kalinsky K, *et al.* Current landscape of immunotherapy in breast cancer: A review. *JAMA Oncol*. 2019; 5: 1205-14.

Afhüppe W, Sommer A, Muller J, *et al.* Global gene expression profiling of progesterone receptor modulators in T47D cells provides a new classification system. *J Steroid Biochem Mol Biol.* 2009; 113: 101-15.

Allan GF, Tsai SY, Tsai MJ, *et al.* Ligand-dependent conformational changes in the progesterone receptor are necessary for events that follow DNA binding. *Proc Natl Acad Sci USA* 1992; 89: 11750-4.

Allison KH, Hammond MEH, Dowsett M, *et al*. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. *J Clin Oncol*. 2020; 38: 1346-66.

André F, Circules E, Rubovszky G, *et al.* Alpelisib for PIK3CA-mutated, hormone receptor–positive advanced breast cancer. *N Engl J Med.* 2019; 380: 1929-40.

Arnett-Mansfield RL, DeFazio A, Mote PA, *et al.* Sub-nuclear distribution of progesterone receptors A and B in normal and malignant endometrium. *J Clin Endocrinol Metabol.* 2004; 89: 1429-42.

Arnett-Mansfield RL, Graham JD, Hanson AR, *et al.* Focal sub-nuclear distribution of progesterone receptor is ligand dependent and associated with transcriptional activity. *Mol Endocrinol.* 2007; 21: 14-29.

Bakker GH, B Setyono-Han, H Portengen, *et al.* 1989. Endocrine and anti-tumor effects of combined treatment with an antiprogestin and antiestrogen or luteinizing hormone-releasing hormone agonist in female rats bearing mammary tumors. *Endocrinology* 1989; 125: 1593– 8.

Ballaréé C, Uhrig M, Bechtold T, *et al.* Two domains of the progesterone receptor interact with the estrogen receptor and are required for progesterone activation of the c-Src/Erk pathway in mammalian cells. *Mol Cell Biol*. 2003; 23: 1994–2008.

Bardia A, Kalamani V, Wilks S, *et al.* Phase I Study of Elacestrant (RAD1901), a novel selective estrogen receptor degrader, in ER-positive, HER2-negative advanced breast cancer. *J Clin Oncol*. 2021; 39(12): 1360-1370.

Beck CA, Zhang Y, Weigel N, *et al.* Two types of anti-progestins have distinct effects on site-specific phosphorylation of human progesterone receptor. *J Biol Chem* 1996; 271: 1209-17.

Bellance C, JA Khan, G Meduri, *et al.* Progesterone receptor isoforms PRA and PRB differentially contribute to breast cancer cell migration through interaction with focal adhesion kinase complexes. *Mol Biol Cell*. 2013; 24: 1363-74.

Bellet Ezquerra M, Morales Murillo S, Gasol Cudos A, *et al.* SOLTI-1802 ONAWA trial: A window of opportunity trial of onapristone (ONA) in postmenopausal women with estrogen and progesterone receptor-positive/HER2-negative (ER+/PgR+/HER2-) early breast cancer (EBC). *Annals of Oncology* 2021; 32, S36.

Beral V and the Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003; 362: 419-27

Bessone MID, Gattas MJ, Laporte M, *et al.* The tumor microenvironment as a regulator of endocrine resistance in breast cancer. *Front Endocrinol* 2019; 10: 547.

Bidard F-C, Kaklamani VG, Neven P, *et al*. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: Results from the randomized phase III EMERALD trial. *J Clin Oncol*. 2022; 10.1200/JCO.22.00338.

Boonyaratanakornkit V, ScottMP, RibonV, *et al.* Progesterone receptor contains a proline-richmotif that directly interacts with SH3 domains and activates c-Src family tyrosine kinases. *Mol Cell*. 2001; 8: 269–280.

Boonyaratanakornkit V, McGowan E, Sherman L, *et al*. The role of extranuclear signaling actions of progesterone receptor in mediating progesterone regulation of gene expression and the cell cycle. *Mol Endocrinol*. 2007; 21: 359–375.

Chandarlapaty S, D Chen, W He, *et al.* Prevalence of *ESR1* Mutations in Cell-Free DNA and Outcomes in Metastatic Breast Cancer: A Secondary Analysis of the BOLERO-2 Clinical Trial. JAMA Oncol. 2016; 2: 1310-5.

Clemm DL, Sherman S, Boonyaratanakornkit V *et al.* Differential hormone dependent phosphorylation of progesterone receptor A and B forms revealed by a phosphoserine site-specific monoclonal antibody. *Mol Endocrinol* 2000; 14: 52-65.

Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Published: November 27, 2017. https://ctep.cancer.gov/protocoldevelopment/electronic applications/docs/ CTCAE_v5_Quick_Reference_5x7.pdf. Site accessed August 7, 2022.

Conlan MG, de Vries EFJ, Glaudemans A, *et al.* Pharmacokinetic and pharmacodynamic studies of elacestrant, a novel oral selective estrogen receptor degrader, in healthy post-menopausal women. *Eur J Drug Metab Pharmacokinet*. 2020; 45: 675-89.

Cottu PH, Bonneterre J, Varga A, *et al.* Phase I study of onapristone, a type I antiprogestin, in female patients with previously treated recurrent or metastatic progesterone receptor-expressing cancers. *PLOS ONE* 2018: 13: e0204973.

Cristofanilli M, Turner NC, Bondarenko I, *et al.* Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2- negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol.* 2016;17: 425-39.

Daniel AR, CA Lange. Protein kinases mediate ligand-independent derepression of sumoylated progesterone receptors in breast cancer cells. *Proc Natl Acad Sci U S A*. 2009; 106: 14287–92.

Daniel AR, Gaviglio AL, Knutson TP, *et al.* Progesterone receptor-B enhances estrogen responsiveness of breast cancer cells via scaffolding PELP1- and estrogen receptor-containing

transcription complexes. Oncogene 2015; 34: 506–15.

De Amicis F, Zupo S, Panno ML, *et al*. Progesterone receptor B recruits a repressor complex to a half-PRE site of the estrogen receptor alpha gene promoter. *Mol Endocrinol*. 2009; 23: 454-65.

Dustin D, Gu G, Fuqua SAW. *ESR1* mutations in breast cancer. *Cancer* 2019; 125: 3714-28.

Dwyer AR, Truong TH, Ostrander JH, *et al*. 90 Years of progesterone: Steroid receptors as MAPK signaling sensors in breast cancer: let the fates decide. *J Mol Endocrinol*. 2020; 65: T35-T48.

Dwyer AR, Truong TH, Kerkvliet CP. Insulin receptor substrate-1 (IRS-1) mediates progesterone receptor-driven stemness and endocrine resistance in oestrogen receptor+ breast cancer. British Cancer 2021; 124: 217–27.

Eisenhauer EA, Therasse P, Bogaerts J, *et al*. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45: 228-47.

El Etreby MF, Liang Y. Effect of antiprogestins and tamoxifen on growth inhibition of MCF-7 human breast cancer cells in nude mice. *Breast Cancer Res Treat* 1998; 49:109-17.

El Etreby MF, Liang Y, Wrenn RW, *et al*. Additive effect of mifepristone and tamoxifen on apoptotic pathways in MCF-7 human breast cancer cells. *Breast Cancer Res Treat*. 1998; 51(2):149-68.

Esber N, Le Billan F, Resche-Rigon M, *et al.* Ulipristal acetate inhibits progesterone receptor isoform a-mediated human breast cancer proliferation and BCl2-L1 expression. *PloS one* 2015; 10, e0140795.

Faivre EJ, Lange CA. Progesterone receptors upregulate Wnt-1 to induce epidermal growth factor receptor transactivation and c-Src-dependent sustained activation of Erk1/2 mitogen-activated protein kinase in breast cancer cells. *Mol Cell Biol* 2007; 27:466-80.

Fei F, Siegal GP, Wei S. Characterizing clinicopathologic features of estrogen receptor-positive/progesterone receptor-negative breast cancers. *Clinical Breast Cancer* 2022, in press.

Ferlay J, Colombet M, Soerjomataram I, *et al*. Cancer statistics for the year 2020: An overview. *Int. J. Cancer* 2021; 149: 778–89.

Finlay-Schultz J, Gillen AE, Brechbuhl HM, *et al.* Breast cancer suppression by progesterone receptors is mediated by their modulation of estrogen receptors and RNA polymerase III. *Cancer Res*. 2017; 77: 4934-46.

Finn RS, Crown JP, Ettl J, *et al*. Efficacy and safety of palbociclib in combination with letrozole as first-line treatment of ER-positive, HER2-negative, advanced breast cancer: expanded analyses of subgroups from the randomized pivotal trial PALOMA-1/TRIO-18. *Breast Cancer Res*. 2016; 18: 67.

Finn RS, Martin M, Rugo HS, *et al*. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med*. 2016; 375: 1925-36.

Gaddy VT, Barrett JT, Delk JN, *et al.* Mifepristone induces growth arrest, caspase activation, and

apoptosis of estrogen receptor-expressing, antiestrogen-resistant breast cancer cells. *Clin Cancer Res*. 2004; 10; 5215-25.

Giulianelli S, JP Vaque, R Soldati, *et al.* Estrogen receptor alpha mediates progestin-induced mammary tumor growth by interacting with progesterone receptors at the cyclin D1/MYC promoters. *Cancer Res*. 2012 ; 72: 2416–27.

Goodman ML, GM Trinca, KR Walter, *et al.* Progesterone receptor attenuates STAT1-mediated IFN signaling in breast cancer. *J Immunol*. 2019; 202: 3076-86.

Graham JD, Hanson AR, Croft AJ *et al.* Nuclear matrix binding is critical for progesterone receptor movement into nuclear foci. *FASEB J* 2009; 23: 543-56(b).

Gupta A, R Mehta, F Alimirah, *et al.* Efficacy and mechanism of action of proellex, an antiprogestin in aromatase overexpressing and letrozole resistant T47D breast cancer cells. *J Steroid Biochem Mol Biol*. 2013 ; 133:30–42.

Gupta N and D Mayer. Interaction of JAK with steroid receptor function. *JAKSTAT* 2013; 2: e24911.

Hagan CR, Regan TM, Dressing GE, *et al*. ck2-dependent phosphorylation of progesterone receptors (PR) on Ser81 regulates PR-B isoform-specific target gene expression in breast cancer cells. *Mol Cell Biol* 2011; 31: 2439-52.

Haque M, Desai KV. Pathways to endocrine therapy resistance in breast cancer. *Frontiers in Endocrinology* 2019; 10: 573.

Hegde SM, Kumar MN, Kavya K, *et al.* Interplay of nuclear receptors (ER, PR, and GR) and their steroid hormones in MCF-7 cells. *Mol Cell Biochem*. 2016; 422: 109-120.

Hilton HN, Graham JD, Clarke CL. 2015. Minireview: progesterone regulation of proliferation in the normal human breast and in breast cancer: A tale of two scenarios? *Mol Endocrinol*. 29: 1230-42.

Hissom JR, Moore MR. Progestin effects on growth in the human breast cancer cell line T-47D--possible therapeutic implications. *Biochem Biophys Res* Commun. 1987; 145: 706-11.

Hosseini H, MMS Obradović, Hoffmann M, *et al.* Early dissemination seeds metastasis in breast cancer. *Nature* 2016, 540: 552-8.

International Agency for Research on Cancer, World Health Organization, Global Cancer Observatory. https://gco.iarc.fr/ accessed August 7, 2022.

Jang GR, Benet LZ. Antiprogestin pharmacodynamics, pharmacokinetics, and metabolism; implications for their long-term use. *J Pharmacokin Biopharmaceut.* 1997; 25: 647-72.

Johnston S, M Martin, A Di Leo, *et al.* MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. *NPJ Breast Cancer* 2019; 5: 5.

Jonat W, Bachelot T, Ruhstaller P *et al.* Randomized phase 2 study of lonaprisan as second line therapy for progesterone receptor positive breast cancer. *Ann Oncol* 2013; 24: 2543–8.

Jonat W, Giurescu M, Robertson JFR. The clinical efficacy of progesterone antagonists in breast cancer. *Endocrine Therapy of Breast Cancer* 2002; Chapter 8:117-24.

Kirsh V, Kreiger N. Estrogen and estrogen-progestin replacement therapy and risk of postmenopausal breast cancer in Canada. *Cancer Causes Control*. 2002; 13: 583-90.

Klein-Hitpass L, Cato ACB, Henderson D; *et al*. Two types of antiprogestins identified by their differential action in transcriptionally active extracts from T47D cells. *Nucleic Acids Research* 1991; 19: 1227-34.

Klijn JG, B Setyono-Han, JA Foekens. Progesterone antagonists and progesterone receptor modulators in the treatment of breast cancer. *Steroids* 2000; 65: 825-30.

Knutson TP, AR Daniel, D Fan, *et al.* Phosphorylated and sumoylation-deficient progesterone receptors drive proliferative gene signatures during breast cancer progression. *Breast Cancer Res*. 2012; 14: R95.

Knutson TP, Truong TH, Ma S, *et al.* Posttranslationally modified progesterone receptors direct ligand-specific expression of breast cancer stem cell-associated gene programs. *J Hematol Oncol* 2017; 10: 89.

Konan, HP, L Kassem, S Omarjee, *et al.* ERα-36 regulates progesterone receptor activity in breast cancer. *Breast Cancer Res* 2020; 22, 50.

Kowalczyk W, Waliszczak G, Jach R, *et al.* Steroid receptors in breast cancer: Understanding of molecular function as a basis for effective therapy development. *Cancer* 2021; 13: 4779

Kuang, Y, B Siddiqui, J Hu, *et al.* Unraveling the clinicopathological features driving the emergence of *ESR1* mutations in metastatic breast cancer. *NPJ Breast Cancer* 2018 ; 4: 22.

Kumar M, K Salem, JJ Jeffery, *et al.* Longitudinal molecular imaging of progesterone receptor reveals early differential response to endocrine therapy in breast cancer with an activating *ESR1* mutation. *J Nucl Med*. 2021; 62: 500-6.

Lamb CA, Helguero LA, Giulianelli S, *et al.* Antisense oligonucleotides targeting the progesterone receptor inhibit hormone-independent breast cancer growth in mice. *Breast Cancer Res* 2005; 7: R1111-21.

Lanari C, Lamb CA, Fabris VT, *et al.* The MPA mouse breast cancer model: evidence for a role of progesterone receptors in breast cancer. *Endocr Relat Cancer*. 2009; 16: 333-50.

Lanari C, V Wargon, P Rojas, AA Molinolo. Antiprogestins in breast cancer treatment: are we ready? *Endocr Relat Cancer* 2012; 19: R35-50.

Lange CA. Integration of progesterone receptor action with rapid signaling events in breast cancer model. *J Steroid Biochem Mol Biol* 2008; 108: 203–12.

Li, W, X Shi, Y Xu, *et al.* Tamoxifen promotes apoptosis and inhibits invasion in estrogen-positive breast cancer MCF-7 cells. Molecular Medicine Reports 2017; 16: 478-484.

Liang Y, Besch-Williford C, Brekken RA, Hyder SM. Progestin-dependent progression of human

breast tumor xenografts: a novel model for evaluating antitumor therapeutics. *Cancer Res*. 2007; 67: 9929–36.

Liang Y, I Benakanakere, C Besch-Williford, *et al.* Synthetic progestins induce growth and metastasis of BT-474 human breast cancer xenografts in nude mice. Menopause2010; 17: 1040.

Liu R, Zhou Z, Zhao D, *et al.* The induction of KLF5 transcription factor by progesterone contributes to progesterone-induced breast cancer cell proliferation and dedifferentiation. *Mol Endocrinol*. 2011; 25: 1137-44.

McFall T, B McKnight, R Rosati, *et al.* Progesterone receptor A promotes invasiveness and metastasis of luminal breast cancer by suppressing regulation of critical microRNAs by estrogen. J Biol Chem. 2018; 293: 1163-77.

Michna H, Schneider MR, Nishino Y, et al. Antitumor activity of the antiprogestins ZK 98.299 and RU 38.486 in hormone dependent rat and mouse mammary tumors: mechanistic studies. *Breast Cancer Res Treat*. 1989 ; 14: 275–88.

Michna H, Gehring S, Kühnel W, *et al*. The antitumor potency of progesterone antagonists is due to their differentiation potential. *J Steroid Biochem Mol Biol*. 1992; 43: 203-10.

Migliaccio A, Piccolo D, Castoria G, *et al.* Activation of the Src/p21ras/Erk pathway by progesterone receptor via cross-talk with estrogen receptor. *EMBO J.* 1998; 17: 2008–18.

Ming J, Cronin SJF, Penninger JM. Targeting the RANKL/RANK/OPG axis for cancer therapy. *Front Oncol*. 2020; 10: 1283.

Mohammed H, Russell IA, Stark R, *et al.* Progesterone receptor modulates Erα action in breast cancer. *Nature* 2015; 523: 313-7.

Montecchia MF, Lamb C, Molinolo AA, *et al.* Progesterone receptor involvement in independent tumor growth in MPA-induced murine mammary adenocarcinomas. *J Steroid Biochem Mol Biol* 1999; 68: 11-21.

Mote P and Clarke C. Relative expression of progesterone receptors A and B in premalignant and invasive breast lesions. *Breast Cancer Res.* 2000; 2(S1): 21-2.

Musgrove EA, RL Sutherland. Biological determinants of endocrine resistance in breast cancer. *Nat Rev Cancer* 2009; 9: 631–43.

Nardone A, De Angelis C, Trivedi MV, *et al.* The changing role of ER in endocrine resistance. *Breast* 2015 ; 24 (Suppl 2): S60-6.

National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program. https://seer.cancer.gov/statfacts/html/breast.html. Accessed August 7, 2022.

Nishino Y, Ishibashi K, Hirtreiter C *et al.* Potentiation of the antitumor effect of tamoxifen by combination with the antiprogestin onapristone. *J Ster Biochem Mol Biol* 2009; 116:187-90.

Nishino, Y, MR Schneider & H Michna. Enhancement of the antitumor efficacy of the antiprogestin, onapristone, by combination with the antiestrogen, ICI 164384. *J Cancer Res Clin*

Oncol. 1994; 120 : 298–302.

Nordenskjöld A, Fohlin H, Fornander T, *et al.* Progesterone receptor positivity is a predictor of long-term benefit from adjuvant tamoxifen treatment of estrogen receptor positive breast cancer. Breast Cancer Res Treat. 2016 ; 160: 313-22.

O'Leary B, Cutts RJ, Liu Y, *et al.* The genetic landscape and clonal evolution of breast cancer resistance to palbociclib plus fulvestrant in the PALOMA-3 trial. *Cancer Discov.* 2018; 8: 1390-403.

Paakinaho V, Palvimo JJ. Genome-wide crosstalk between steroid receptors in breast and prostate cancers. *Endocr Relat Cancer* 2021; 28: R231-50.

Parise CA and V Caggiano. Breast cancer survival defined by the ER/PR/HER2 subtypes and a surrogate classification according to tumor grade and immunohistochemical biomarkers. *J Cancer Epidemiol*. 2014; 2014: 469251.

Patel, HK, N Tao, KM Lee. *et al.* Elacestrant (RAD1901) exhibits anti-tumor activity in multiple ER+ breast cancer models resistant to CDK4/6 inhibitors. *Breast Cancer Res. 2019;* 21**,** 146.

Proietti CJ, C Rosemblit, W Beguelin, *et al.* Activation of Stat3 by heregulin/ErbB-2 through the co-option of progesterone receptor signaling drives breast cancer growth. *Mol Cell Biol*. 2009; 29: 1249–65.

Pucci B, Kasten M, Giordano A. Cell cycle and apoptosis. *Neoplasia* 2000; 2:291-9.

Rayasam GV, Elbi C, Walker DA *et al.* Ligand-specific dynamics of the progesterone receptor in living cells and during chromatin remodeling *In vitro*. *Mol Cell Biol.* 2005; 25: 2406-18.

Renema N, B Navet, MF Heymann, *et al.* RANK-RANKL signalling in cancer. *Biosci Rep*. 2016; 36: e00366.

Robert, C. A decade of immune-checkpoint inhibitors in cancer therapy. *Nat Commun*. 2020; 11: 3801.

Robertson JFR, Willsher PC, Winterbottom L, *et al.* Onapristone, a progesterone receptor antagonist, as first-line therapy in primary breast cancer. *Europ J Cancer* 1999; 35: 214-8.

Rojas PA, M May, GR Sequeira, *et al.* Progesterone Receptor Isoform Ratio: A Breast Cancer Prognostic and Predictive Factor for Antiprogestin Responsiveness. *J Natl Cancer Inst*. 2017; 109: djw317.

Rosati, R, K Oppat, Y Huang, *et al.* Clinical association of progesterone receptor isoform A with breast cancer metastasis consistent with its unique mechanistic role in preclinical models. BMC Cancer 2020; 20: 512.

Sasaki M, Tanaka Y, Perinchery G *et al.* Methylation and inactivation of estrogen, progesterone, and androgen receptors in prostate cancer. *J Natl Can Inst* 2002; 94: 384-90.

Scarpin KM, Graham D, Mote PA *et al.* Progesterone action in human tissues: regulation by progesterone receptor (PR) isoform expression, nuclear positioning and coregulator expression.

Nuclear Receptor Signaling 2009; 7: 1-13.

Schairer C, Lubin J, Troisi R, *et al*. Estrogen-progestin replacement and risk of breast cancer. JAMA. 2000; 284: 691-4.

Sequeira GR, A Sahores, Dalotto-Moreno T, *et al.* Enhanced Antitumor Immunity via Endocrine Therapy Prevents Mammary Tumor Relapse and Increases Immune Checkpoint Blockade Sensitivity. *Cancer Res*. 2021; 81: 1375-87.

Simon R. Optimal two-stage designs for phase II clinical trials. *Controlled Clinical Trials* 1989; 10: 1-10.

Singhal H, Greene ME, Zarnke AL, *et al.* Progesterone receptor isoforms, agonists and antagonists differentially reprogram estrogen signaling. *Oncotarget* 2017; 9: 4282-300.

Singhal H, Greene ME, Tarulli G, *et al.* Genomic agonism and phenotypic antagonism between estrogen and progesterone receptors in breast cancer. *Sci Adv* 2016; 2: e1501924.

Slamon DJ, Neven P, Chia S, *et al.* Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med* 2020; 382: 514-24.

Tanos T, Sflomos G, Echeverria PC *et al.* Progesterone/RANKL is a major regulatory axis in the human breast. *Science Translational Medicine* 2013; 5: 182ra55

Thomas, M, Monet J-D. Combined effects of RU486 and tamoxifen on the growth and cell cycle phases of the MCF-7 cell line. *J Clin Endocrinol Metab* 1992; 75: 865–70.

Truong TH, Dwyer AR, Diep CH, *et al*. Phosphorylated progesterone receptor isoforms mediate opposing stem cell and proliferative breast cancer cell fates. *Endocrinology* 2019; 160: 430–46.

Truong TH and Lange CA. Deciphering steroid receptor crosstalk in hormone-driven cancers. *Endocrinology* 2018; 159: 3897-907.

Turner NC, Slamon DJ, Jungsil R, *et al.* Overall survival with palbociclib and fulvestrant in advanced breast cancer. *N Engl J Med*. 2018; 379: 1926-36.

Walter KR, Balko JM, and Hagan CR. Progesterone receptor promotes degradation of STAT2 to inhibit the interferon response in breast cancer. *Oncoimmunology 2020;* 9: e1758547.

Walter KR, Goodman ML, Singhal H, *et al.* Interferon-stimulated genes are transcriptionally repressed by PR in breast cancer. *Mol Cancer Res*. 2017; 15: 1331-40.

Werner LR, Gibson KA, Goodman ML, *et al.* Progesterone promotes immunomodulation and tumor development in the murine mammary gland. *J Immunother Cancer*. 2021; 9: e001710.

Wu X, F Li, L Dang *et al.* RANKL/RANK system-based mechanism for breast cancer bone metastasis and related therapeutic strategies. *Front Cell Dev Biol*. 2020; 8: 76.

Yeh WL, Shioda K, Coser KR, *et al.* Fulvestrant-induced cell death and proteasomal degradation of estrogen receptor α protein in MCF-7 cells require the CSK c-Src tyrosine kinase. *PLoS One*. 2013; 8: e60889.

14 APPENDICES

Appendix 1 HBV/HCV Testing Criteria Eligibility based on serologic markers for hepatitis B and hepatitis C

Test	Result				
HBsAg	+	-	-	-	-
HBcAb	Any	+	-	+	-
HBsAb	Any	-	+	+	-
HCV Ab	Any	Any	-	-	-
Eligibility	Not Eligible	Not Eligible	Eligible	Eligible	Eligible

If indeterminate results are obtained, viral DNA (hepatitis B) or RNA (hepatitis C) should be measured to confirm negative viral status.

HBsAg positive: Indicates active infection and risk for reactivation with fulminant hepatitis. These patients are not eligible for this trial.

HBcAb positive and HBsAb negative: indicate active infection and risk for reactivation. These patients are not eligible for this trial.

HBsAb positive: As a standalone marker, it indicates successful vaccination or previous infection that has been successfully resolved if it is the only positive finding. These patients are eligible for this trial.

HBsAg negative, HBcAb positive, HBsAb positive: Resolved or latent infection. These patients are eligible for this trial.

All markers negative: No prior exposure or vaccination to hepatitis B and no prior exposure to Hepatitis C. Patients are eligible for this trial

HCV Ab positive: Indicates active infection and risk for reactivation. These patients are not eligible for this trial.

Appendix 2 ECOG Performance Status Criteria

ECOG Performance Status Scale	
Grade	**Descriptions**
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction
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)
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
3	In bed >50% of the time Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair
5	Dead

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