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Cover Page

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Systems Biology Guided Therapy for Breast Cancer Positive for Oestrogen Receptor after Aromatase Inhibitor and CDK inhibition.

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Historical Protocol Versions
Version 1: 4/12/21
Version 2: 8/16/2022
Version 3:

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LIST OF ABBREVIATIONS

Abbreviation or Term[1]	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AV	Atrioventricular
β-HCG	Beta-human chorionic gonadotropin
BID	Twice daily
BLQ	Below limit of quantification
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca^{++}	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
Cl-	Chloride
CL_{cr}	Creatinine clearance
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events

Abbreviation or Term[1]	Definition/Explanation
CV	Coefficient of variation
CYP	Cytochrome P450
D/C	Discontinue
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
Eg	Exempli gratia (for example)
FACS	Fluorescence Activated Cell Sorting
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose (FDG)-positron emission tomography (PET)
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GLP	Good laboratory practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCO_3^-	Bicarbonate
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
hr	Hour or hours
IC_{50}	Half maximal inhibitory concentration
i.e.	Id est (that is)
IEC	Independent ethics committee
INR	International normalized ratio
IRB	Institutional review board
IU	International unit

Abbreviation or Term[1]	Definition/Explanation
IV	Intravenous, intravenously
LDH	Lactate dehydrogenase
LLQ	Lower limit of quantitation
MedRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic resonance imaging
MRSD	Maximum recommended starting dose
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect-level
PD	Pharmacodynamic(s)
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QC	Quality control
RBC	Red blood cell
QD	Once daily
QTc	QT interval corrected
QTcF	QT interval corrected using Fredericia equation
SAE	Serious adverse event
SD	Standard deviation or stable disease
$T_{1/2}$	Terminal elimination half-life
T_3	Triiodothyronine
T_4	Thyroxine
T_{max}	Time of maximum observed concentration
TID	Three times daily

Abbreviation or Term[1]	Definition/Explanation
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
ULQ	Upper limit of quantitation
UV	Ultraviolet
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of nonchildbearing potential

All of these abbreviations may or may not be used in protocol.

PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the course of the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

_____ _____

Signature of Principal Investigator **Date**

_____

Principal Investigator Name (Print)

_____

Name of Institution

STUDY SUMMARY

Title	Systems Biology Guided Therapy for Breast Cancer Positive for Oestrogen Receptor after Aromatase Inhibitor and CDK inhibition.
Short Title	*SPOCK*
Protocol Identifiers (IRB – internal)	U21-02-4401
IND number	*N/A*
Phase	II
Design	Open label, interventional All patients will have a biopsy at the beginning of the trial. The biopsy will be sent for DNA sequencing through FoundationOne (clinical test) and RNA profiling at Fulgent (research test) for determination of activation of various oncogenic pathways and phenotypes. The results will be analyzed by Dr. Nath and Dr. Bild, and a treatment recommendation will be made to the treating physician based on the algorithm below. Biopsies will also be performed 2-4 weeks after the start of therapy for correlative purposes.
Study Duration	24 months recruitment, with up to 3 years of follow up per patient
Objectives	**Primary** To determine if systems biology guided therapy can improve PFS **Secondary** To determine the minimum turn-around time needed for systems biology analysis To determine the response rate to systems biology guided therapy To compare PFS based on concordance with recommended treatment
Number of Subjects	74 treated according to recommendations
Diagnosis and Main Eligibility Criteria	• Metastatic or incurable breast cancer • Progression while on aromatase inhibitor and CDK inhibitor

	• Biopsiable lesion • ECOG 0-2 • Age 18 or greater
Study Product, Dose, Route, Regimen	Drug determined by treating oncologist based on recommendation from systems biology analysis.
Duration of administration	Until intolerance or progression.
Reference therapy	Unguided therapy
Statistical Methodology	The PFS will be compared to 8 months, which is the approximate expected median PFS of fulvestrant +/- alpelisib as second line unguided therapy after AI+CDK inhibitor based on SOLAR-1. With a two-sided alpha of 0.1, beta of 0.2, 18 months of accrual, and 6 months of follow-up, 74 patients are needed to detect a 4 month improvement in PFS with genomic - guided therapy.

1 OBJECTIVES

1.1 Primary Objectives and Endpoint

1.1.1 Primary Objective

To determine if systems biology guided therapy can improve PFS

1.1.2 Primary Endpoint

Progression free survival in patients treated in concordance with recommendation

1.2 Secondary Objectives

To determine the minimum turn-around time needed for systems biology analysis
To determine the response rate to systems biology guided therapy
To compare PFS based on concordance with recommended treatment

2 BACKGROUND

Over 70% of breast cancers are positive for estrogen receptors (ER+) and do not overexpress HER2 (HER2-). These tumors are driven by estrogen and addicted to estrogen signaling, so the primary treatment for metastatic ER+, HER2- treatment is estrogen blockade. Because of the results of the PALOMA-1, MONALEESA-2, and MONARCH-3 trials, the standard of care for first-line treatment of metastatic ER+, HER2- breast cancer is aromatase inhibitor plus a CDK4/6 inhibitor(1)

The second line treatment for ER+, HER2- breast cancer is less well defined. Multiple mechanisms of resistance to aromatase inhibitors or CDK4/6 inhibitors have been described. These include ligand-independent activation of ER through increased tyrosine kinase signaling, mutations in the alpha isoform of ER, deregulated ER co-regulators, epigenetic changes, and activation of PI3K/AKT/MTOR signaling.(2) The only available tests are for mutations in these various genes, and of these only mutations in PIK3CA have been shown to be clinically useful.(3)

The NCCN lists multiple options for second-line therapy of ER+, HER2- metastatic breast cancer after progression on aromatase inhibitor plus CDK4/6 inhibitors.(1) These include fulvestrant, a selective estrogen degrader, fulvestrant plus alpelisib, a PI3K inhibitor approved only when PIK3CA is mutated, exemestane plus everolimus, an MTOR inhibitor, tamoxifen, or chemotherapy. There is no biologic way to choose among these options in the absence of a PIK3CA mutation.

Gene expression profiling has become commonly used in early-stage breast cancer but is not commonly used in metastatic breast cancer. Therefore, we have developed gene expression-based biomarkers of estrogen activation in advanced breast cancer and of MTOR activation in breast cancer. We hypothesize that treatment based on these biomarkers can improve progression free survival by matching treatments to tumors with active pathways targeted by those treatments. The algorithm for treatment recommendations is shown in figure 1.

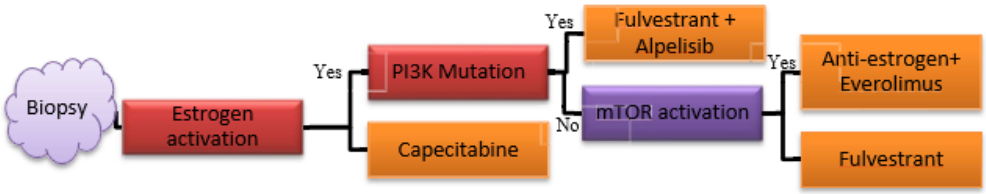

Figure 1: Algorithm for Treatment Recommendations

ENDORSE

ENDORSE is a 63-gene gene expression signature to measure estrogen signaling in metastatic breast cancer. It was derived from 833 ER+, HER2- tumors from METABRIC, a database of gene expression data for breast cancer. ENDORSE was validated in data from an independent cohort assessing 140 patients with metastatic ER+ breast cancer treated with endocrine therapy, over three quarters of which had received prior endocrine therapies. ENDORSE was able to separate those with short survival with endocrine therapy from those with long survival (figure 2). ENDORSE was also validated by showing it could predict the decrease in Ki-67 in two neoadjuvant trials of fulvestrant. ENDORSE is not predictive in HER2+ or ER- breast cancers, showing it is a true marker of estrogen signaling activation.

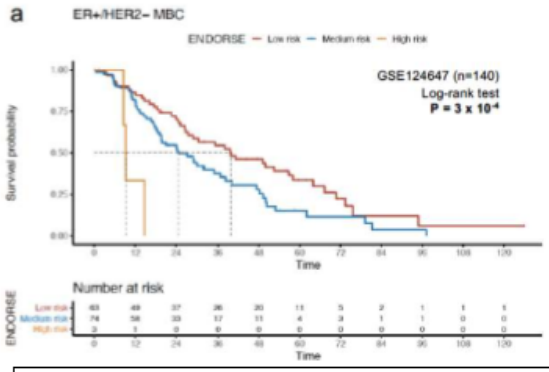

Figure 2: Survival after endocrine therapy for women with metastatic ER-positive, Her2-negative breast cancer based on classification by the ENDORSE signature of estrogen pathway activation. Low Risk = High estrogen activation, High Risk = low estrogen activation.

MTOR Signature

No datasets exist with gene expression data from patients with ER+ breast cancer treated with MTOR inhibitors. (BOLERO-2 collected gene expression data but due to consent issues that data has now been destroyed). Therefore, we derived the MTOR signature from gene expression data combining data from a clinical trial of everolimus in the neoadjuvant treatment of breast cancer with in vitro drug sensitivity data from a panel of 9 cell lines. We used machine learning to develop a 97-gene gene expression signature for predicting the ability of everolimus to decrease proliferation in breast tumors. Results of internal validation are shown in the figure. Since no other dataset exists with gene expression data in metastatic breast cancer prior to treatment with everolimus, no MTOR signature can be externally validated. Because exemestane/everolimus and fulvestrant are both FDA approved in the population eligible for SPOCK and this is not a curable population, we consider it appropriate to proceed

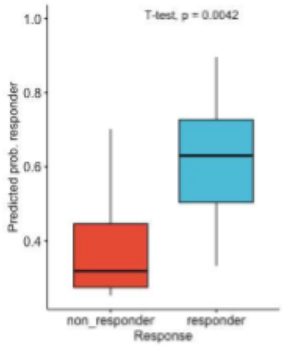

Figure 3: Boxplots comparing predicted probability of mTOR inhibitor response in ER+ breast cancers grouped by observed clinical response to everolimus plus aromatase inhibitor.

without external validation, noting that this trial will provide a dataset that can be used for validation of predictors by us and others in the future.

3 DRUG INFORMATION

N/A

4 STUDY DESIGN

4.1 Description

Single-arm, open label phase II trial.

4.2 Number of Patients

66 evaluable patients, 74 total to account for dropout

4.3 Number of Study Centers

2-5

4.4 Study Duration

24 months of recruitment. Maximum 3 years of follow up.

5 ELIGIBILITY CRITERIA

This eligibility checklist is used to determine patient eligibility and filed with signature in the patient research chart.

Patient No. _____
Patient's Initials: (L,F,M) _____

5.1 **Inclusion Criteria**
Yes/No (Response of "no" = patient ineligible)

_____ Histologic diagnosis of breast cancer (ER+, HER2-)
_____ Metastatic or incurable
_____ Prior treatment with an antiestrogen and a CDK4/6 inhibitor
_____ Progression while on or within 6 months of stopping the CDK4/6 inhibitor
_____ At least one lesion amenable to percutaneous biopsy (bone lesions are allowed as long as they are clearly progressive from tumor)
_____ ECOG 0-2
_____ Age 18 or greater
_____ Able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

5.2 **Exclusion Criteria**
Yes/No (Response of "yes" = patient ineligible)
_____ Prior treatment within 2 years with alpelisib, everolimus,
_____ Comorbid disease other than breast cancer with a life expectancy of less than 2 years
_____ Cancer other than breast cancer that is expected to need treatment within 2 years
_____ Platelets < 100,000/microliter
_____ INR > 1.5

I certify that this patient meets all inclusion and no exclusion criteria for enrollment onto this study.

_____
Investigator Signature **Date**

_____
Coordinator Signature **Date**

_____
Coordinator Signature Date

6 TREATMENT PLAN

6.1 Patient enrollment

Once a patient signs the informed consent form, she/he may be screened. If all inclusion/exclusion criteria are met, then they are enrolled. During screening a biopsy site will be identified. In accordance with the ASCO Ethical Framework for Mandatory Research Biopsies, because the biopsy results are used in the primary endpoint of the study, the biopsy risk may be low or moderate risk (expected rate of major complications < 1.5%), including biopsy of bone marrow, skin, superficial masses, intra-abdominal masses, peripheral thoracic masses that can be accessed without penetrating lung, or sites that will be biopsied for other clinical purposes.

Note that after patients may be continued on the most recent therapy up to the biopsy at the discretion of the treating oncologist. After the biopsy, the treating oncologist may opt to start a new therapy while waiting for results and then switch based on results if desired. No wash-out period necessary.

6.2 Tissue collection

Once a participant is registered, a biopsy site will be identified, and a biopsy will be scheduled. The biopsy sample will be processed per the lab manual. The sample will be sent to City of Hope, where RNA will be extracted. The RNA will be sent to Fulgent Laboratories, which is a CLIA –certified laboratory, for analysis. Residual tissue or RNA will be preserved and stored in the Center for Hope Translational Core Laboratory for correlative studies.

6.3 Results and data collection

The assay results from Fulgent will be reported on the SPOCK report form, which will be transmitted to the principal investigator who will ensure copies are given to the treating physician and the data team. The principal investigator will be responsible for linking the participant's study ID on the report form to the participant's identity. The dates on which the biopsy was done and on which the report is given to the treating physician will be recorded.

Participants will be followed every 3 months for up to 3 years to determine length of treatment, reason for discontinuation, and progression free survival.

6.4 Duration of Study

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

- Subject withdraws consent from the study treatment and/or study procedures. A subject must be removed from the trial at his/her own request or at the request of his/her legally acceptable representative. At any time during the

trial and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.

- Subject is lost to follow-up.
- Death.

Subjects may be withdrawn from the study for the following reasons:

- The subject is non-compliant with trial procedures.
- If, in the investigator's opinion, continuation of the trial would be harmful to the subject's well-being.

7 TOXICITIES AND DOSEAGE MODIFICATION

Because all drugs are FDA-approved for this indication and are being prescribed consistent with their label, the only AEs collected will be those related to the biopsy. Dose modifications will be at the discretion of prescribing physician based on standard practice.

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for adverse event and serious adverse event reporting. A copy of the CTCAE Version 5.0 can be downloaded: (**http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx**).

All supportive measures consistent with optimal patient care will be given throughout the study.

8 STUDY CALENDAR

MONTHLY Calendar

Examination	Pre-study[1] (≤ 28 days of signed consent)	After registration	4-8 weeks after start of therapy[5]	Every 3 months (+/- 1 month)[4]	M9D1 (+/- 1 month)	EOT[3]
Informed consent	X					
Medical history	X					
Eligibility criteria	X					
Vital signs	X	X				
Physical examination	X					X
Study blood tube[2]		X	X[5]		X	X
CBC	X					
PT/INR	X					
Biopsy		X	X[5]			X[3]
Restaging Scans				X[4]		X

1 ALL Pre-study/Screening procedures should be completed within 4 weeks of study enrollment - with the exception of laboratory tests which need to be completed within 2 weeks prior to study enrollment.

2 Study blood tube: One lavender top 10 ml tube and one red/gray top 8.5ml tube

3 End of treatment biopsy is optional

4. Restaging scans are recommended to include a chest/abdomen/pelvis CT and either bone scan or PET scan at least every 3 month (+/- 1 month). MRI is an acceptable substitute for CT. After 15 months they can be done at a frequency of the prescriber's discretion.

5. Week 6 blood and biopsy can be done at least 4 weeks and no more than 8 weeks after start of therapy. Start of therapy is defined as the first day of drug taken by the patient after delivery of the biopsy report to the treating oncologist.

9 CRITERIA FOR EVALUATION AND ENDPOINT

9.1 Efficacy

The following definitions and criteria (RECIST version 1.1)(4) should be used for the baseline evaluations of existing disease, and for the ongoing evaluation of tumor responses.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter (LD) ≥ 10 mm using CT, MRI, or caliper measurements or ≥20 mm with x-ray. Although brain metastases are allowable, no brain lesion will be a TARGET lesion but can be followed as Non-Target.

Non-measurable lesions - all other lesions including small lesions (LD < 10 mm with CT, MRI, or caliper measurements or <20 mm with x-ray).

Documentation of "Target" and "Non-Target" Lesions

- All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.
- Target lesions should be selected based on their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinical assessments).
- A sum of the LD for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference by which to characterize the objective tumor response.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

9.1.1 Response Criteria

	Evaluation of target lesions
Complete Response (CR)	Disappearance of all target lesions (Must persist for a minimum of four weeks)
Partial Response (PR)	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD (Must persist for a minimum of four weeks)
Progressive Disease (PD)	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

	Evaluation of non-target lesions
Complete Response (CR)	Disappearance of all non-target lesions
Stable Disease (SD)	Persistence of one or more non-target lesion(s)
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

9.1.2 Evaluation of Best Overall Response

The best overall response is the best response observed until progression/recurrence and is determined as indicated in the table below:

Target Lesions	Non-Target Lesions	Evaluation of New Lesions	Best Overall Response
CR	CR	No	CR
CR	SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

9.1.3 Progression Free Survival

Progression free survival will be determined from the day the biopsy result report is given to the treating oncologist until the date of progression or death, whichever comes first, by RECIST 1.1.

Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST v1.1 assessment.

For the primary analysis, patients who change therapy for reasons other than RECIST 1.1 progression will be censored at the time of starting new therapy, but a sensitivity analysis will be performed counting these as progression events. Patients who continue on therapy at the discretion of the treating oncologist but who have progression by RECIST 1.1 will be considered to have progressed and will have end of treatment (EOT) procedures done.

9.2 Safety

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, and clinical laboratory test results. More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator.

Physical Examination

Complete and symptom-directed physical examinations will be performed by a licensed physician (or physician's assistant or nurse practitioner).

Vital Signs

Vital signs (blood pressure, respiratory rate, pulse rate and temperature) will be obtained in the sitting position. Patients should be sitting for 3-5 minutes prior to obtaining vital signs.

Safety Laboratory Determinations

Laboratory evaluations will be performed as noted in the flow chart.

10 STATISTICAL CONSIDERATIONS

10.1 Sample size determination

This is an open-label phase II study of systems biology guided therapy for breast cancer patients positive for Oestrogen receptor after Aromatase inhibitor and CDK inhibition. Based on the SOLAR-1 trial, 25% of tumors would have PIK3CA mutation, so 25% of people would be treated with fulvestrant plus alpelisib with a median PFS in that group of 11 months and 75% of people would be treated with fulvestrant with a median PFS in that group of 6 months.(3) The weighted average of these medians is 7.25 months, but since the actual distributions of the progression free survivals are not available, we will use a conservative estimate of the expected median PFS of the historical control group (fulvestrant +/- alpelisib as second line unguided therapy) of 8 months.

Based on the preclinical assessments and assay features, it is expected that 10% of patients enrolled in the trial will be assigned to capecitabine, 25% to fulvestrant/alpelisib, 32.5% to fulvestrant, and 32.5% to exemestane everolimus. The goal is to assign people to therapy so that the capecitabine group will have a median PFS of 18 months (75th percentile of survival in BOLERO-6(5)), the fulvestrant group will have a median PFS of 10 months (75^{th} percentile of survival in SOLAR-1(3)), and the exemestane/everolimus group will have a median PFS of 13 months (25^{th} percentile of BOLERO-2(6)). From the results of the BOLERO-2 trial, BOLERO-6 trial, and the SOLAR-1 trial, it is hypothesized that the weighted median PFS with genomic- guided therapy will be improved to 12.1 months from 9 months of fulvestrant +/- alpelisib as second line unguided therapy after AI+CDK inhibitor.

With an alpha of 0.1, beta of 0.2, 18 months of accrual, and 6 months of follow-up, 66 patients are needed to detect a 4-month improvement in the median PFS (from 8 months to 12 months) with genomic- guided therapy, assuming an exponential distribution using a 2-sided Log-rank test. Accounting for 10% loss, the trial will enroll 74 eligible patients.

10.2 Statistical Analysis

10.2.1 Primary Endpoint

Progression Free Survival (PFS)

PFS is defined as the time from the time results are given to the treating oncologist to the first occurrence of disease progression or death from any cause (whichever occurs first) according to RECIST 1.1. Patients without disease progression or death at the time of analysis will be censored at the last disease assessment date from their last evaluable RECIST v1.1 assessment.

For the primary objective, all enrolled patients who receive therapy concordant with the genomic recommendation will be evaluable for analysis. Concordant therapy will be any anti-estrogen plus any PI3K inhibitor in the "fulvestrant plus alpelisib" group, any anti-estrogen plus any MTOR inhibitor in the "exemestane plus everolimus" group, any antiestrogen in the "fulvestrant" group, and any cytotoxic chemotherapy in the "capecitabine" group.

The PFS curve will be estimated using the Kaplan-Meier product-limit method. Two-sided, 95% CI for the median PFS will be computed by the Brookmeyer and Crowley method with log-log transformation.

10.2.2 Secondary Endpoints

Turn-around time needed for systems biology analysis

The turn-around time is defined as time from when patient's biopsy sample is shipped until the time when the report is sent. The turn-around time will be summarized by the range, mean, median, and STD.

Objective Response Rate (ORR)

The ORR is defined as the proportion of participants who achieve either a complete response or PR, as defined by BICR using RECIST v1.1. The ORR will be estimated and its 2-sided 95% CIs will be calculated using the Clopper-Pearson exact method.

PFS

As defined previously. Log-rank test will be used to compare the PFS of patients who receive the treatment recommended by the genomic analysis with those who are given a different treatment.

10.2.3 Safety analysis

Safety analyses will be based on all biopsied subjects. Only AEs related to the biopsies will be reported. Safety data will be summarized using descriptive statistics. Categorical

variables will be summarized by number and percentage. Continuous variables will be summarized using n (number of subjects with available data), mean, standard deviation, median, upper and lower quartiles, and range (minimum and maximum), unless otherwise specified.

11 REGISTRATION GUIDELINES

Patients must meet all of the inclusion and none of the exclusion criteria listed in Section 5 prior to registration.

Study related screening procedures can only begin once the patient has signed a research consent form. Patients must not begin protocol treatment prior to registration.

After informed consent is signed, patient eligibility is determined during the screening period by the study team. When all screening procedures are complete, eligibility must be confirmed by three people, one of whom is an investigator. Once the eligibility review is signed by all three study team members, it is documented in the relevant patient records and the patient study status is changed from screening to treatment in the RedCap. The patient is then registered to this study. No treatment may begin unless this process has occurred.

12 DATA SUBMISSION SCHEDULE

The Case Report Forms (CRFs) are a set of (electronic or paper) forms for each patient that provides a record of the data generated according to the protocol. CRF's will be created prior to the study initiation and updated (if applicable) when amendments to the protocol are approved by the respective IRB. **Data capture will be restricted to endpoints and relevant patient information required for planned manuscripts.** These forms will be completed throughout the study. The medical records will be source of verification of the data. During the study, the CRFs will be monitored for completeness, accuracy, legibility, and attention to detail by a member of the Quality Management Specialist at the Inova Schar Cancer Institute. The CRFs will be completed by a member of the study team as listed on the Delegation of Authority Log. The data will be reviewed no less than annually by the Inova Schar Cancer Institute Data and Safety Monitoring Committee. The Investigator will allow the Data and Safety Monitoring Committee or Research Compliance Office personnel access to the patient source documents, clinical supplies dispensing and storage area, and study documentation for the above-mentioned purpose. The Investigator further agrees to assist the site visitors in their activities.

13 SPECIAL INSTRUCTIONS

13.1 Biopsy samples

A total of THREE core tumor samples should be collected per patient at each time point (baseline, week 6, optional EOT) using core needle (minimum 18 gauge, preferable 14 gauge)

Tumor samples will be processed per the lab manual. One core sample will be formalin fixed and paraffin embedded for immunohistochemical analysis.

One core sample will be placed in a labeled cryotube containing tissue preservation media and flash frozen in liquid nitrogen for at least 15 minutes and then stored at -70 or -80 degrees.

One core sample will be placed in OCT medium in an OCT cassette. The cassette will then be frozen in liquid nitrogen for 15 minutes and then stored at -70 or -80 degrees.

13.1.1 Time points
Baseline and week 6, optional EOT

13.1.2 Required Forms

Each sample collection container (tube, syringe, etc) and storage device (cryotubes, etc) must be minimally labeled with:

- Study name: SPOCK
- Subject ID number: 3 digit site number + 3 digit patient number
- Date of collection
- Time of collection (24-hour clock)
- Sample time point, e.g., Cycle 1 Day 1 PK sample

Please ensure that the sample information, i.e. date and time of collection, is identical to that captured in source documents.

14 CONSIDERATIONS

14.1 **Informed consent**
Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB approved version.

14.2 **Institutional Review**
Study will be approved by the Western Institutional Review Board.

Data and Safety Monitoring Plan

This study meets the Inova Schar Data Safety and Monitoring Committee (ISCI DSMC) definition for low risk. All low risk studies are audited no less than annually by the ISCI DSMC and audit reports will be reviewed and approved by the full ISCI DSMC. The DSMC will also review all Serious Adverse Events for patients on this study.

14.3 **Adverse Events / Serious Adverse Events**

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for AE and SAE reporting. An electronic copy of the CTCAE Version 5.0 can be downloaded from:
http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx

14.3.1 Adverse Events (AE)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Adverse Events will be collected only if they are related to the study biopsies.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit or phone contact during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. the severity grade based on CTCAE v.5 (grade 1-5)
2. its relationship to the study procedure (definite, probable, possible, unlikely, not related)
3. its duration (start and end dates or if continuing at final exam)
4. action taken (no action taken; non-drug therapy given; drug-therapy given; hospitalization/prolonged hospitalization)
5. whether it constitutes an SAE

All adverse events will be treated appropriately. Once a related adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

All adverse events will be immediately recorded in the patient research chart.

14.3.2 Serious Adverse Event (SAE)

Information about all serious adverse events within 30 days of a study biopsy will be collected and recorded. A serious adverse event is an undesirable sign, symptom, or medical condition which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- causes congenital anomaly or birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition

Adverse events which fall within the definitions listed above must be reported as an SAE regardless, if they are felt to be related or not.

14.4 **SAE Reporting Requirements**

SAEs must be reported to the DSMC and the IRB, according to the requirements described below:

IRB Notification:

- Events meeting the IRB of record reporting requirements will be submitted through the IRB's electronic reporting system within the current published timeline required by IRB.
- External sites should abide by local IRB requirements for submission of SAEs

*Medwatch 3500A form can be found at http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/ucm082728.pdf

14.5 **Reporting of Pregnancy**

Although pregnancy is not considered an adverse event, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject, including the pregnancy of a male subjects' female partner as an SAE. Pregnancies or lactation that occurs during the course of the trial or with 30 days of completing the trial or starting another new anticancer therapy, whichever is earlier, must be reported to the DSMC, IRB, FDA, and the sponsor as applicable. All subjects and female partners who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events.

14.6 **Protocol Amendments**

Any amendments or administrative changes in the research protocol during the period, for which the IRB approval has already been given, will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial.

14.7 **Protocol Deviations**

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The IRB requires the **prompt reporting** of protocol deviations which are:

- Exceptions to eligibility criteria.
- Intended to eliminate apparent immediate hazard to a research participant or
- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm), or
- Possible serious or continued noncompliance

14.8 **Clinical Trials Data Bank**

The study will be registered on **http://clinicaltrials.gov** and the NCI CTRP (Clinical Trials Reporting Program) by the Inova Schar Clinical Trials Office.

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AS MODIFIED
Sep 18, 2022

Informed Consent for a Research Study

TITLE:	Systems Biology Guided Therapy for Breast Cancer Positive for Oestrogen Receptor after Aromatase Inhibitor and CDK inhibition.
PROTOCOL NO.:	U21-02-4401 WCG IRB Protocol #20212138
SPONSOR:	Inova Schar Cancer Institute
PRINCIPAL INVESTIGATOR:	Adam L. Cohen, MD, MS
RESEARCH LOCATIONS:	**Inova Schar Cancer Institute** 8081 Innovation Park Drive Fairfax, VA 22031 **Inova Schar Cancer Institute Fair Oaks** 3580 Joseph Siewick Drive, Suite 403 Fairfax, VA 22033 **Inova Schar Cancer Institute Mark Center** 1800 N Beauregard Street, Suite 350 Alexandria, VA 23111
STUDY RELATED PHONE NUMBER(S):	571-472-4724 (24 hours)

KEY INFORMATION ABOUT THE STUDY:
You are being invited to take part in a research study. A research study is different from the regular medical care you receive from your doctor. The research is designed to learn new information. Taking part in the research is voluntary. This form contains important information that will help you decide whether to participate in the study. Take the time to carefully review this form. You should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others such as your family, friends, or other doctors about joining this study.

Purpose of the study

- The purpose of this study is testing an investigational new way of determining the best treatment in breast cancer
- This study will take up to 3 years including follow up
- This study will include a biopsy with a report to your doctor, who will then decide how to use that information in your treatment

Possible Risks and Discomforts

This study has the following possible risks:

The biopsy could cause bleeding, infection, or damage to an organ.

A breach of our data systems could cause loss of confidentiality.

There may be risks that are unknown at this time.

Potential Benefits of Being in the Study

- The benefits of participation are that your doctor will get information about the biology of your cancer that may help them select treatments for you now or down the line.
- This study will help doctors learn more about metastatic ER-positive breast cancer and this information may help in the treatment of future patients.

Alternatives to Being in the Study

- Instead of being in this study, you can choose not to have the biopsy in the study and have a treatment or a testing for your cancer you and your doctor decide on.
- If you decide that you don't want any more active treatment, one of your options is called "comfort care." Comfort care includes pain medication and other support. It aims to maintain your comfort and dignity rather than cure disease. Usually, this care can be provided at home. If you think you might prefer comfort care, please discuss this with your family, friends and your doctor.

Other Important Information

1. WHY IS THIS STUDY BEING DONE?

There are several approved and guideline-recommended treatments for metastatic, estrogen receptor-positive breast cancer that has progressed on an aromatase inhibitor and a CDK4/6 inhibitor. Right now, doctors do not have a good way of choosing between these treatments. Scientists we work with have come up with ways to use the biology of the tumor to try to predict which treatment is best. This study is being done to test if those predictions are right and to learn more about these tumors to design better treatments in the future.

2. WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

If you consent to participate in this study, you will have a physical examination and two tubes of blood drawn to assess your risk of bleeding. If you qualify for the trial, you will then have a biopsy of your cancer. The site of the biopsy will be determined by the study investigators. The biopsy will involve being stuck by a needle three times to obtain tissue. An ultrasound or a CT scan may be done to guide the needle. The tissue will then be processed and sent to labs for analysis. Two more tubes of blood will be drawn at the time of the biopsy. About 2 weeks after

the biopsy, a report will be sent to your doctor with predictions for what treatment is best for you. Your doctor will discuss those predictions with you and decide with you on your next treatment. Six weeks after you have been on treatment you will have a second biopsy and two more tubes of blood drawn. The study team will access your medical records over the next 3 years to see how long you are on this treatment. If your tumor grows again you can choose to have another biopsy for further analysis.

Biobanking: Biological specimens (such as blood, tissue, or saliva) will be collected and shared with an outside lab or collaborator for analysis. The specimens will not be identifiable. The specimens will be banked for future use.

Data Collection: Data will be collected and shared with an outside collaborator for analysis. The data will not be identifiable. The data will be banked for future use.

3. HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY

About 74 people will take part in this study as a whole.

4. CAN I STOP BEING IN THE STUDY?

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. Your decision will not affect your future relationship with Inova or the study doctor.

5. WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THE STUDY?

Your participation in this study is voluntary. You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled.

6. WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

The biopsies and blood draws will be paid for by the study. All research analysis will be paid for by the study. Some analyses, including a test called FoundationOne, are approved tests and will be billed to your insurance. There is no compensation for participation in this study.

7. WHAT IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

If you believe you have been injured as a direct result of participating in this study, treatment will be provided. You should contact the Principal Investigator, Adam L. Cohen at 571-472-4724 (24-hour). The charges for any medical treatment you receive will be billed to you or your insurance carrier. You will be billed for any amount your insurance does not cover.

Inova and the study doctor do not routinely provide funds or free medical treatment for injuries that result from taking part in this study. There are no plans to pay you for lost wages, disability, or discomfort. However, by signing this form you have not given up any of your legal rights.

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8. WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

Effort will be made to keep your records private to the amount allowed by law. Research records are stored and kept according to legal requirements. You will not be identified in any reports or publications about this study. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Also, your records may be reviewed by the following groups:

- Office of Human Research Protections or other federal, state or international regulatory agencies;
- The Inova Institutional Review Board or Office of Research;
- The sponsor of the study, their agents or study monitors;
- U.S. Food and Drug Administration;
- Your insurance company (if charges are billed to insurance)
- Members of the study staff;
- Additional groups, explained in the HIPAA Authorization for Research form may also have access to these records.

If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic, or physician's office records. Authorized Inova staff not involved in the study may be aware that you are participating in a research study and have access to your information.

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

You will also be asked to sign a separate Health Insurance Portability and Accountability Act (HIPAA) research authorization form if the study involves the use of your protected health information.

9. WILL DATA (AND BIOSPECIMENS) FROM THIS STUDY BE USED OR SHARED FOR FUTURE RESEARCH?

Your data and/or samples may be stored and shared for future research without additional informed consent if identifiable private information, such as your name and medical record number, are removed. Once your identifying information is removed from your data [and/or samples], we will no longer be able to identify and destroy them.

The use of your samples may result in commercial profit. You will not be compensated for the use of your samples other than what is described in this consent form.

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10. WILL THE RESEARCHERS PROVIDE INFORMATION TO ME ABOUT WHAT THEY LEARN FROM MY PARTICIPATION IN THIS STUDY?

When results from this study are published, we will mail you a copy of the results. This may not be for several years.

11. WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this study is voluntary. You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

If you decide to withdraw from the study, it will not be possible to remove or destroy the samples and/or data that have already been collected.

No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose access to medical care or forfeit legal rights to which you are otherwise entitled. A member of your research team will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

12. WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

You can talk to your study doctor about any questions, complaints or concerns you have about this study. Contact your study doctor Adam L. Cohen, MD, MS at 571-472-4724 (24-hours).

An Institutional Review Board is a group responsible for overseeing the protection of human research participants. If you have any questions or concerns about your rights as a research subject or if you have any questions, concerns or complaints about the research study, you may also contact the Institutional Review Board (IRB) at (855) 818-2289, or researchquestions@wcgirb.com

If you would like more information about your rights as a participant in a research study, you may also contact Inova's Human Research Protection Office (HRPO) at 1-888-534-6682.

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SIGNATURE
I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had the questions answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this form.

Signature of Subject

Printed Name of Subject

Date

Investigator/Research Staff

I have explained the purpose, the procedures, the benefits and risks that are involved in this research study before requesting the signature(s) above. Any questions that have been raised have been answered to the individual's satisfaction. A copy of this form has been given to the participant or his/her representative.

Signature of Person Obtaining Consent
Consent

Printed Name of Person Obtaining

Date

The following witness lines may be left blank, unless an impartial witness is required.*

Signature of Impartial Witness

Printed Name of Impartial Witness

Date

*An impartial witness, **who is a witness to the informed consent process that is not involved in the conduct of the research**, is required when a non-English speaking subject is encountered, an interpreter is used, and consent is documented through the use of a short form or when the subject cannot read the consent form.