NOVARTIS

Clinical Development

Ribociclib (LEE011)

Protocol CLEE011AUS42 / NCT03050398

A companion sample collection protocol to support the discovery of breast cancer aberrations with treatment of CDK4/6 therapy/LEE011/Ribociclib

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List of abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area Under the Curve
BC	Breast Cancer
BCRP	Breast Cancer Resistance Protein
IRC	Independent Review Committee
BSEP	Bile Salt Export Pump
BUN	Blood Urea Nitrogen
CBR	Clinical Benefit Rate
CCND1	Cyclin D1
CDK4/6	Cyclin-Dependent Kinases 4 and 6
Cmax	Peak blood concentration
Cmin	Minimum concentration
CR	Complete Response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCR	Disease Control Rate
DDI	Drug-Drug Interaction
DILI	Drug-Induced Liver Injury
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
DS&E	Drug Safety and Epidemiology
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EOT	End of Treatment
ER	Estrogen Receptor
FAS	Full Analysis Set
FFPE	Formalin-Fixed, Paraffin-Embedded
FIH	First-in-human
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
HDL	High Density Lipoprotein
HER2	Human Epidermal Growth Factor Receptor 2
HIV	Human Immunodeficiency Virus
HR+	Hormone Receptor Positive
IB	Investigator Brochure

IC50	Inhibitory Concentration, where 50% inhibition is observed
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LFT	Liver Function Test
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
LVEF	Left Ventricular Ejection Fraction
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation
MBC	Metastatic Breast Cancer
MTD	Maximum Tolerated Dose
MUGA	Multiple Gated Acquisition
NCRNPD	Non-Complete Response Non-Progressive Disease
NSAI	Nonsteroidal Aromatase Inhibitors
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall survival
PAS	Pharmacokinetic Analysis Set
Pd	Pharmacodynamics
PD	Progressive Disease
PFS	Progression free survival
P-gP	Permeability-glycoprotein
PgR	Progesterone receptor
PHI	Protected Health Information
PK	Pharmacokinetics
PPS	Per Protocol Set
PR	Partial Response
pRb	Retinoblastoma Protein
PS	Performance Status
PT	Prothrombin time
QD	Quaque Die (every day)
RAP	Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
RDE	Recommended dose of expansion
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
R Value	ALT/ALP in x ULN
SAE	Serious Adverse Event

[redacted]

SC	Steering Committee
SD	Stable Disease
SEC	Safety Event Categories
SERM	Selective ER Modulators
S-ICF	Study ICF
SMT	Novartis Safety Management Team
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1/2	The elimination half-life associated with the terminal slope (z) of a semi logarithmic concentration-time curve (time).
TBIL	Total Bilirubin
ULN	Upper Limit of Normal

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when a patient permanently discontinues study treatment for any reason
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.

[redacted]

Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of Consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

[redacted]

Synopsis

Title	A companion sample collection protocol to support the discovery of breast cancer aberrations with treatment of/LEE011/Ribociclib
Sponsor and Clinical	Novartis – Region US
Phase	I/II
Investigation/Study Type	Interventional
Purpose and Rationale	The purpose of this US only companion sample collection protocol of the Global Phase IIIb trial (CLEE011A2404) is to (1). investigate the aberrations of common pathways for HR+ breast cancer at baseline in all consented patients enrolled in this companion sample collection protocol (2). evaluate genetic mutations in tumor following the progression on ribociclib (3). assess various mutations in diverse patient populations at diagnosis (4). [redacted]
Primary Objective(s)	Determine the various modes of resistance to ribociclib following progression of disease.
Secondary Objectives	Secondary: - To assess the mutational aberrations across a diverse patient population with newly diagnosed HR+ HER2- advanced breast cancer. [redacted]
Study Design and Assessments	This is a multicenter, US specific, non-treatment based companion sample collection protocol. This protocol will evaluate the aberrations of common pathways for newly diagnosed HR+/HER2- advanced breast cancer tumors and responses to ribociclib in diverse patient populations. This companion sample collection protocol is available for all US patients enrolled on CLEE011A2404 (CompLEEment-1) and will not alter the planned treatment. Tumor collection required for this study will occur at two time points: at baseline/screening and upon the development of progressive disease as shown in Section 7.2. The analyses of samples will be conducted in an on-going fashion as tumor tissue from patients becomes available. Sites will be provided with the results the genetic mutation profiles of their patients' tumor upon progression.

[redacted]

	The baseline/screening tumor sample (metastatic site preferred) should be obtained during the screening process for the CLEE011A2404 study prior to starting the investigational drug regimen. However, a window of one month into study treatment will be permitted if not possible to obtain a fresh tumor tissue sample during the screening period so as to not delay study treatment. If fresh tissue is unavailable, archival tissue from the primary or metastatic site (metastatic site preferred) will then be acceptable (and may be sent in after the start of study treatment to allow for logistic planning of obtaining the archival sample). The second tumor tissue sample will be obtained at time of progression and prior to subsequent therapy. 
Population	Patients enrolled in the United States to protocol CLEE011A2404 (a study that includes men and postmenopausal women with HR+, HER2- aBC who had not received any prior hormonal agent for treatment of advanced disease).
Key Inclusion criteria	Patients eligible for this companion sample collection protocol sample collection protocol must meet all inclusion in CLEE011A2404.
Key Exclusion criteria	Patients eligible for this companion sample collection protocol must not meet any of the exclusion criteria in the CLEE011A2404 study, in addition to the following: 1. Patients without either fresh or archival tumor tissue accessible.
Investigational and reference therapy	Ribociclib 600mg oral daily (3 weeks on/ 1 week off) in combination with letrozole 2.5 mg oral once daily
Statistical methods	Details of the analyses including primary analysis to be will be described in a corresponding statistical analysis plan.

1 Background

1.1 Overview of current treatment

Breast cancer is the most common malignancy in women in the US and the leading cause of cancer deaths in women worldwide. Hormone receptor positive breast cancer is the most common form of breast cancer. In the overall patient population, it is estimated that 246,660 women will be diagnosed with breast cancer this year and 39,620 will die from it. Breast cancers are heterogeneous and exist in many different subtypes, characteristics, responses to treatment, and patient outcomes. Breast cancer ranks second as a cause of cancer death in women after lung cancer.[1] Subtypes of breast cancer are classified by the presence of estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2) antigens as well as by distinct gene expression profiles[9,12] and other features for prognostic and treatment purposes. Seventy percent of invasive breast cancers in women >45 years of age, express ER and/or PgR, but not HER2, and are termed hormone receptor positive HER2 negative (HR+/HER2-).[4]

2 Rationale

2.1 Study rationale and purpose

Despite the advances in treatment, resistance to single agent endocrine therapy is a well-established barrier, leading to many patients progressing within approximately 1-year of first-line treatment.[3,7,8] Patient treatment is currently guided by hormone receptor status and HER2 expression, but accumulating evidence suggests that genetic mutations also influence drug responses and patient survival.[10] Thus, identifying the unique gene mutation pattern in each breast cancer subtype will further improve personalized treatment and outcomes for breast cancer patients.

Currently there is no clinical data available reporting reasons for tumor progression following treatment with a CDK 4/6 inhibitor, which represents an unmet need and requires further exploration. There are multiple potential reasons why a patient would progress on CDK 4/6 inhibitor + endocrine combinations. These may include loss or mutation of retinoblastoma protein (Rb) (the direct target of CDK 4/6 inhibitors), alterations in the estrogen receptor pathway as a consequence of endocrine resistance, or activation of other signaling pathways including the PI3K/AKT/mTOR pathway. The heterogeneity of the anticipated mechanism of resistance requires further exploration through analysis of the tumor following progression of a CDK 4/6 inhibitor.[6]

Despite improvement in diagnosis and treatment, racial disparities are prominent. Survival is lower for both African American and Hispanic women at every stage of diagnosis compared to Caucasian women. The 2008–2012 age-adjusted breast cancer incidence rate for Caucasian women in the United States was 128.1 per 100,000 women compared to 124.3 for African American women, 91.9 for Native American women, 91.9 for Hispanic women, and 88.3 for Pacific Islander women, per 100,000 women. For the same time period, the mortality rates were 21.9 per 100,000 women for Caucasian women compared to 31 for African American

[redacted]

women, 14.5 for Hispanic women, 15 for Native American women, and 11.4 for Pacific Islander women, per 100,000 women.[1] Thus, while Caucasian women are more likely to be diagnosed with breast cancer, African American women are more likely to die from it. For all stages combined, the 5-year relative survival rate is 90% for Caucasian women and 79% for African American women. Hispanic women are about 20% more likely to die of breast cancer than non-Hispanic Caucasian women diagnosed at a similar age and stage.[13]

While the reason for this disproportionate death due to breast cancer for African American and Hispanic women is multi-fold and therefore being studied at many institutions, there is still a lack of understanding of genetic mutations and their role. Whole-exome sequencing data from the tumors of African American and Caucasian women diagnosed with breast cancer between 1988 and 2013 (a group of 105 African American and 664 Caucasian patients) from the National Cancer Institute's Cancer Genome Atlas showed that the same five tumor-specific mutations were most prevalent among both groups. However, more African American patients' tumors were driven by the TP53 mutation, while the PIK3CA mutation was more common among the tumors of Caucasian patients.[5]

The purpose of this US only companion sample collection protocol of the Global Phase IIIb trial (CLEE011A2404) is to (1). investigate the aberrations of common pathways for HR+ breast cancer at baseline in all consented patients enrolled (2). evaluate genetic mutations in tumor following the progression on ribociclib (3). assess various mutations in diverse patient populations at diagnosis (4). [redacted]

2.2 Rationale for study design

Tumor tissue samples will be collected in this trial at baseline to identify biomarkers that may be predictive of benefit from the combination of ribociclib and letrozole, understand the mutations present in newly diagnosed advanced breast cancer patients and to understand the heterogeneity of mutations across diverse patient populations. Tumor samples will also be collected at time of progression (End of Treatment). This will be done using both Nanostring and multiplexed approaches (Next Gen Sequencing) of but not limited to CCND1, CDKN2A, PIK3CA and PTEN as well as protein expression profiling of PDL-1 and CD8 using AQUA (Automated Quantitative Analysis), a fluorescent IHC. The biopsy collected at progression/end of treatment will be dedicated to understanding resistance to treatment of ribociclib in combination with letrozole as well as immune profiling of this patient population. This study also provides a unique opportunity to investigate the various mutations in a heterogeneous patient population with HR+/HER2- advanced breast cancer at initial diagnosis and following progression to CDK4/6 inhibition.

[redacted]

[redacted]

[redacted]

Tumor samples will be requested at baseline and following progression. Tumor tissue samples will be obtained only from patients who consent to participating in this this sample tumor collection and will be sent to a third party central laboratory for analysis. All sites that participate in this study will receive the results of the genetic mutation of their patients' tumor tissue profile upon progression.

3 Objectives and endpoints

This is a non-interventional study to allow for the collection of tumor and normal tissue samples [redacted] to better understand relevant mutations and the mechanisms responsible for resistance to treatment.

	Objective	**Endpoint**
Primary	Determine the various modes of resistance to ribociclib following progression of disease	Mutations of genes that are relevant to HR+ and the CDK4/6 pathway such as but not limited to CCND1, CDKN2A, PIK3CA and PTEN to identify the potential mechanisms of progression.
Secondary	To assess the mutational aberrations across a diverse patient population with newly diagnosed HR+ HER2- advanced breast cancer	Differences in mutations will be assessed based on baseline samples and compared across diverse races/ethnicities with HR+ HER2- advanced breast cancer - specifically Caucasian, African America, Hispanic, Native American and Pacific Islander.

[redacted]

4 Study design

4.1 Description of study design

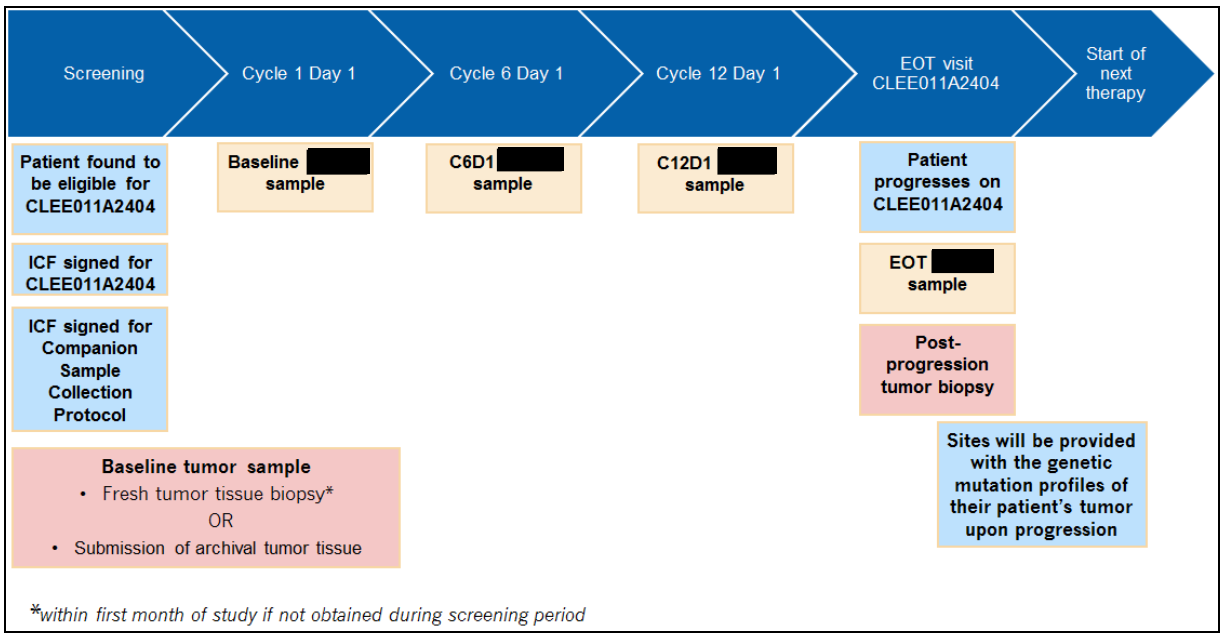
This is a multicenter, US specific, non-treatment based companion sample collection protocol. This protocol will evaluate the aberrations of common pathways for newly diagnosed HR+/HER2- advanced breast cancer tumors and responses to ribociclib in diverse patient populations. This companion sample collection protocol is available for all US patients enrolled on CLEE011A2404 (CompLEEment-1) and will not alter the planned treatment. Tumor collection required for this study will occur at two time points: at baseline/screening and upon the development of progressive disease as shown in Section 7.2. For each tumor tissue sample, three analyses will be conducted (1), using Next Generation Sequencing (NGS): evaluating known human cancer-related genes to assess for genetic alterations and (2) Gene expression analysis using nanostring technology and (3) Protein assessment of PDL-1 and CD8 to evaluate the immune profile of this patient population pre and post-treatment to ribociclib.

The analyses of samples will be conducted in an on-going fashion as tumor tissue from patients becomes available. Sites will be provided with the results of the genetic mutation profiles of their patients' tumor upon progression.

The baseline/screening tumor sample (metastatic site preferred) should be obtained during the screening process for the CLEE011A2404 study prior to starting the investigational drug regimen. However, a window of one month into study treatment will be permitted if not possible to obtain a fresh tumor tissue sample during the screening period so as to not delay study treatment. If fresh tissue is unavailable, archival tissue from the primary or metastatic site (metastatic site preferred) will then be acceptable (and may be sent in after the start of study treatment to allow for logistic planning of obtaining the archival sample). The second tumor tissue sample will be obtained at time of progression and prior to subsequent therapy.

[redacted]

Figure 4-1 Study design



5 Patient population

Men and postmenopausal women with hormone receptor-positive (HR+) HER2-negative (HER2-) advanced breast cancer (ABC) with no prior hormonal therapy for advanced disease.

This US-only companion sample collection protocol is intended to be applied to the CLEE011A2404 study sponsored by Novartis. The investigator or designee must ensure that

[redacted]

only patients who meet the inclusion/exclusion criteria for the CLEE011A2404 protocol can participate.

5.1 Inclusion criteria

Written informed consent must be obtained prior to any baseline/screening procedures.

Patients eligible for this companion sample collection protocol sample collection protocol must meet **all** inclusion in CLEE011A2404.

5.2 Exclusion criteria

Patients eligible for this companion sample collection protocol must not meet **any** of the exclusion criteria in the CLEE011A2404 study, in addition to the following:

1. Patients without either fresh or archival tumor tissue accessible.

6 Treatment

6.1 Study treatment

Patients on this companion sample collection protocol will be treated per the guidelines of the CLEE011A2404 study on the investigational treatment of ribociclib and letrozole.

6.2 Patient numbering

Upon signing the informed consent form, the patient will be given the same unique identification number that corresponds to their patient number on the CLEE011A2404 study.

6.3 Concomitant medications

Concomitant medications and significant non-drug therapies given as treatment for serious adverse events considered by the investigator to be possibly related to the biopsy procedures will be collected as defined in the treatment protocol of main study CLEE011A2404 and documented in the treatment eCRF for CLEE011A2404 (ensuring to document in the eCRF details that this is related to US Companion sample collection protocol CLEE011AUS42).

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. No central laboratory requisition form will be used as a source document.

Table 7-1 Visit evaluation schedule

Visit Name	Protocol Section	Screening	Cycle 1	Cycle 6	Cycle 12	End of Treatment/Progression of Disease

[redacted]

Visit Name	Protocol Section	Screening	Cycle 1	Cycle 6	Cycle 12	End of Treatment/Progression of Disease
Day of Cycle		**-21 to 1**	**1**	**1**	**1**	**within 15 days from the last dose[1]**
Obtain Informed Consent	7.1.1	X				
Tissue collection	7.2.1 7.2.3 7.2.4	X[2]				X
[redacted]						

[1] Tissue sample may be obtained after 15 days if not feasible within 15 days from the last dose. Must be collected prior to starting subsequent therapy.

[2] If not collected during screening, can be collected during the first month of treatment. If fresh tissue sample cannot be obtained, archival sample may be sent in during the first month of treatment.

[redacted]

7.1.1 Screening

The IRB approved Informed Consent Form (ICF) for this companion sample collection protocol, CLEE011AUS42, must be signed and dated before any procedures are performed (procedures that are part of the clinical routine or are described in the CLEE011A2404 protocol may be performed before signing the ICF). A copy of the ICF must be given to the patient or to the person signing the form (if applicable). The Investigator or designee must record the date when the study informed consent was signed in the medical records of the patient as well as on the relevant central laboratory requisition form.

Investigators must assess each patient for risk factors that affect the collection of biopsies according to their usual clinical practice.

7.1.1.1 Screen failures

Patients who sign an ICF but fail to undergo a biopsy (or provide archival tissue) or are otherwise found to be ineligible after signing the study ICF will be considered screen failures for this protocol. Patients identified as screen failures under the treatment protocol CLEE011A2404 will not be enrolled under this protocol.

7.1.2 Patient data to be collected in the central laboratory requisition forms

Data for this companion sample collection protocol will be collected via the central laboratory requisition forms completed for each sample. These requisition forms will document that informed consent has been obtained for participation in this protocol and for storage of biological samples, confirm that the patient met the inclusion/exclusion criteria for CLEE011A2404, and collect information about the lesions biopsied at baseline and upon progression [redacted]. Any adverse events considered by the investigator to be related to the biopsy procedure, should be captured in the CLEE011A2404 study EDC database, with a comment that it is related to the US companion

[redacted]

sample collection protocol CLEE011AUS42. Additional data collected as part of the CLEE011A2404 protocol and needed for the interpretation of the results from the genomic analyses, will also be utilized.

7.1.3 Early study termination, and premature withdrawal

7.1.3.1 Early study termination

This study can be terminated at any time for any reason by Novartis. The investigator will be responsible for informing IRBs of the termination of this study

7.1.3.2 Premature withdrawal

Patients may voluntarily withdraw from either the CLEE011A2404 and/or this study CLEE011AUS42 or be dropped from it at the discretion of the investigator at any time. The reason for discontinuation will be recorded on the applicable corresponding eCRFs in the CLEE011A2404 EDC database (if patient is withdrawn from the CLEE011A2404 study) and captured on the central laboratory requisition form for US companion sample collection protocol CLEE011AUS42.

If a patient withdraws consent, Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date.

If a patient withdraws from the CLEE011A2404 study, the investigator will still receive the output of the data collected from this study up to the time point of the patient's withdrawal.

If a patient withdraws consent, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information. Study treatment must be discontinued and no further assessments conducted.

7.2 Assessment

7.2.1 Assessments in tumor tissue

The tumor sample collections for this study are summarized in Table 7-2.

All assessments will be performed by a Novartis designated central laboratory. Instructions for collection, preparation and shipment can be found in the laboratory manual. Required sample collection information must be entered on the appropriate requisition forms provided by the central laboratory.

Tumor samples will be taken pre-treatment (during screening, with an allowed one month window from C1D1 if unable to obtain during screening), and following progression. Blocks are preferred but if not possible, 20 unstained slides (minimum 15) should be made available for biomarker studies. If a tumor sample is not accessible pre-treatment, an archival sample is allowed (metastatic site preferred). A pathology report must be submitted along with the patient's archival tumor block/slides. Biopsy collection will also be performed at the time of disease progression (and prior to the start of subsequent treatment) for identifying potential markers of lack of response/resistance.

Tumor samples will be tested for genetic and proteomic alterations (e.g., gene expression, mutations, amplifications, deletions and/or protein expression/activation etc.) that are involved in the D-cyclin-CDK4/6-INK4a-Rb and mTOR pathways, such as mutations of CCND1, PIK3CA, PTEN and CDK4, gene amplification of CCND1 and CDK4, deletion of CDKN2A, as well as potential resistant/escape pathways to CDK 4/ 6 inhibitors. Other cancer associated genes will also be investigated in the tumor tissue from all patients, with the intention of understanding potential mechanisms of resistance to prior CDK 4/6 inhibitors. Biomarker analyses will be correlated with clinical outcome to determine potential predictive biomarkers of ribociclib/letrozole response and resistance.

When choosing lesions for biopsy after the development of resistance, a sample from the same lesion chosen at screening/baseline is preferred if the lesion is growing in size, can be identified, and remains accessible to safely biopsy. Detailed instructions for the collection, handling, and shipping of biomarker samples are outlined in the Laboratory Manual.

[redacted]

7.2.3 Secondary analyses in tumor tissue

When remaining samples are available in sufficient quantity and quality, samples may be used to assess the mutational aberrations across a diverse patient population with newly diagnosed HR+ HER2- advanced breast cancer. This will be assessed based on baseline tumor tissue samples and compared across diverse races/ethnicities with HR+ HER2- advanced breast cancer.

[redacted]

[redacted]

Table 7-2 Biomarker collection schedule

Sample Type	Volume	Visit	Sample Collection
Baseline tumor biopsy (Fresh tissue from metastatic site preferred. If fresh tumor is not accessible, archival tissue will be accepted)	Blocks are preferred but if not possible, 20 unstained slides (minimum 15) should be made available.	Screening	Prior to treatment (or within the first month of study). If archival, can be sent in when obtained from sample storage.
Newly obtained post-progression tumor samples)	Blocks are preferred but if not possible, 20 unstained slides (minimum 15) should be made available.	Post- progression	Upon progression (prior to subsequent treatment)
[redacted]			

8 Safety monitoring and reporting

8.1 Serious adverse events

For this companion sample collection protocol sample collection protocol, only serious adverse events considered related to the biomarker collection procedure will be extracted from the AE eCRF of the CLEE011A2404 protocol. All SAEs experienced should be reported in the CLEE011A2404 study EDC system, with a comment that the SAE was related to this US Companion sample collection protocol, protocol CLEE011AUS42.

8.1.1 Serious adverse event definitions

Serious adverse events (SAEs) are defined in the CLEE011A2404 protocol. Those serious adverse events considered by the investigator to be possibly related to a biomarker collection procedure performed as part of this protocol will be indicated as such in the AE eCRF in the CLEE011A2404 EDC system.

8.1.2 Serious adverse event reporting

SAEs will be collected and reported as described in the CLEE011A2404 protocol. If the event is suspected to be causally related to a biomarker collection procedure, as assessed by the investigator, it will be identified as such. SAEs will be followed until resolution or until clinically relevant improvement or stabilization. SAE collection ends 14 days after the last biomarker collection procedure.

[redacted]

Any SAEs experienced after this 14 day period should only be reported to Novartis if the investigator suspects a causal relationship to a biomarker collection procedure performed as part of this companion sample collection protocol. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to the biomarker collection procedures, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

The telephone and telefax number of the contact persons in the local department of Drug Safety and Epidemiology (DS&E), specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to which the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

If the SAE is thought to be related to a biomarker collection procedure performed as part of the CLEE011AUS42 protocol, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in the CLEE011AUS42 study that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

[redacted]

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training. Data from this study will be combined with data from other studies, including but not limited to the treatment study CLEE011A2404 on which the patient received the investigational agent(s).

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and central laboratory requisition forms with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the requisition forms, the adherence to the protocol to Good Clinical Practice and the progress of enrollment. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, and the results of any other tests or assessments. All information recorded on the requisition forms must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the completed central laboratory requisition forms. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the requisition forms are performed according to the study-specific monitoring plan.

9.3 Data collection

Biomarker (blood and tissue) samples drawn during the course of this companion sample collection protocol will be collected from the Investigator sites and analyzed by a Novartis assigned laboratory or contracted central lab. The results will be sent electronically to Novartis. Designated investigational site staff will complete the information required by the protocol into the appropriate central laboratory requisition forms (printed on 2 or 3-part non-carbon-required paper). Field monitors will review the central laboratory requisition forms for accuracy and completeness and instruct site personnel to make any required corrections or additions. One copy of the requisition form will be forwarded to each analytical laboratory

with the respective samples by the designated investigational site staff, and one copy will be retained at the investigational site.

The Principal Investigator is responsible for assuring that the data entered on the central laboratory requisition forms is complete, accurate, and that entry and updates are performed in a timely manner.

10 Statistical methods and data analysis

This companion sample collection protocol seeks to explore the mechanisms of resistance to cancer treatment through the analysis of data from tumor samples at baseline and after development of disease progression, [redacted] Analyses are considered exploratory in nature and the detailed data analysis plan(s) will be described in stand-alone documents or, where appropriate, in the individual Statistical Analysis Plan (SAP) from corresponding parent treatment studies for inclusion in the respective CSRs.

Broadly, data analyses will seek to (1). analyze mutations present at the initial diagnosis of HR+/HER2- advanced breast cancer across diverse ethnicities (2). characterize the mutations identified at progression of disease following the treatment of ribociclib + letrozole and (3). characterize the immune response to ribociclib + letrozole. Descriptive statistics and exploratory modeling will be used. Details will be described in the data analysis plans.

10.1 Analysis sets

The biomarker analysis set (BAS) includes all US subjects with evaluable biomarker assessment from the Full Analysis set of CLEE011A2404 study.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including disease characteristics and prior treatment will be listed and summarized descriptively for the BAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical at baseline will be summarized by system organ class and preferred term.

10.3 Statistical analysis plan

Details of the analyses including primary analysis to be performed will be described in a corresponding statistical analysis plan.

10.4 Safety reporting

10.4.1 Serious adverse events (AEs)

Summary tables for serious adverse events (AEs) have to include only AEs that are only suspected to be related to the biomarker collection procedures in the opinion of the investigator. Biomarker collection-related SAEs will be summarized by system organ class

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and/or preferred term, severity (based on CTCAE grades) and type of serious adverse event. These will be reported in the CLEE011A2404 EDC system with a comment that the SAE is related to the companion sample collection protocol CLEE011AUS42 protocol.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and treatment group.

Review of these safety data will be conducted on an on-going basis by members of the study team. The findings will be documented and will be made available upon request.

10.5 Sample size calculation

Not applicable. All US subjects from CLEE011A2404 will be included in this study.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. 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 Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written, IRB/IEC/REB-approved informed consent.

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. The date when a subject's Informed Consent was actually obtained will be captured in the appropriate central laboratory requisition forms.

Novartis will provide to investigators, in a separate document, a proposed Informed Consent Form (ICF) that is considered appropriate for this study and complies with the ICH GCP guidelines and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB and a

copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

This protocol includes only men and post-menopausal women. However, all participants should be informed that taking the study medication may involve unknown risks to a fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in the clinical study agreement.

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The central laboratory requisition forms are the primary data collection instrument for this companion sample collection protocol. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the requisition forms and all other required reports. Data reported on the requisition forms, which are derived from source documents, should be consistent with the source documents or the

discrepancies should be explained. All data requested on the requisition forms must be recorded. Any missing data must be explained. Any change or correction to a requisition form should be dated, initialed, and explained (if necessary) and should not obscure the original entry. The investigator should retain records of the changes and corrections to the requisition forms.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site, prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB 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

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protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations but not later than 10 working days.

13 References (available upon request)

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4. Huang H, Groth J, Sossey-Alaoui K, Hawthorn L, Beall S, Geradts J. Aberrant expression of novel and previously described cell membrane markers in human breast cancer cell lines and tumors. Clin Cancer Res. 2005 Jun 15;11(12):4357-64.
5. Keenan T, Moy B, Mroz EA, Ross K, Niemierko A, Rocco JW, Isakoff S, Ellisen LW, Bardia A (2015) Comparison of the genomic landscape between primary breast cancer in African American versus white women and the association of racial differences with tumor recurrence. J Clin Oncol 2015(2062):2126.
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8. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines v2.2016: Breast Cancer.
9. Perou CM, Sorlie T, Eisen MB, et al (2000) Molecular portraits of human breast tumours. Nature; 406 (6797):747-752.
10. Reinert T, et al. Optimal management of hormone receptor positive metastatic breast cancer in 2016. *Ther Adv Med Oncol.* 2015;7:304–320.

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13. Williams, F. & Thompson, E. J. Racial and Ethnic Health Disparities (2016) 3: 233. doi:10.1007/s40615-015-0132-9.

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