SCRI DEVELOPMENT INNOVATIONS

Master Statistical Analysis Plan Checklist

for Investigator Initiated Trials

A Phase II Open Label Study of Everolimus in Combination with Anti-estrogen Therapy in Hormone Receptor-Positive HER2-Negative Advanced Breast Cancer

Sponsor:	**Sarah Cannon Development Innovations (Innovations)**
Study Drug:	**Everolimus**
SCRI Protocol Number:	**BRE 212**
NCT number:	**02291913**
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Date	**06DEC2019**

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History of Changes

This document has undergone the following changes:

Version Number	Version Date	Description of Changes
1.0	31MAY2018	Original document
2.0	06DEC2019	Formatting; textual clarifications with respect to protocol; and TFL output duplicate remediation with renumbering

1.1 Objectives	
Primary Objective:	To determine the efficacy of everolimus in combination with anti-estrogen therapy in patients with ER and/or PR-positive, HER2-negative advanced breast cancer demonstrating disease progression on prior hormonal therapy as measured by PFS
Secondary Objectives:	To determine the safety and tolerability of everolimus with an anti-estrogen therapy in patients with ER and/or PR-positive, HER2-negative advanced breast cancer
Exploratory Objectives:	To evaluate the VeriStrat assay in this HR-positive patient population treated with everolimus in combination with anti-estrogen therapy
1.2 Study Design	
Study Type	☒ Non-Randomized ☐ Randomized (Allocation Ratio:)
Details	This is a multi-centered, open-labeled, Phase II study in MBC. The patient population includes locally recurrent or MBC patients with cytologically or histologically confirmed hormone receptor-positive breast cancer who have demonstrated disease progression on prior anti-estrogen therapy or therapies. Eligible patients must have evaluable or measurable disease per RECIST v1.1. Progression Free Survival (PFS), defined as the time from the first day of study drug administration (Day 1) to disease progression (event) as defined by the RECIST v1.1 criteria, or death (event) on study. Patients who are alive and free from disease progression will be censored at the date of last tumor assessment. Patients who receive non-protocol therapy (subsequent therapy) prior to incurring an event will be censored at the date of last tumor assessment prior to the start of subsequent therapy. Patients who do not have a post-baseline tumor assessment will be censored at the date of first treatment (Day 1). Overall Survival (OS), defined as the time from the first day of study drug administration (Day 1) or death on study. Patients who are alive will be censored at the date of last known date alive. Duration of Response (DOR), is defined as the time from the first date of CR or PR to disease progression or death as defined by the RECIST v1.1 criteria. Patients who are alive and free from disease progression will be censored at the date of last tumor assessment. Patients who receive non-protocol therapy (subsequent therapy) prior to incurring an event will be censored at the date of last tumor assessment prior to the start of subsequent therapy. Only those patients who achieved CR or PR will be included in the summaries of DOR. PFS (efficacy primary endpoint), OS and DOR (efficacy secondary endpoints) estimates will be generated using Kaplan-Meier methods, both for all patients enrolled and those patients receiving the MTD. Four month and six month PFS estimates with 95% confidence intervals (CIs), and median PFS and OS with 95% CIs, will be calculated. Best overall response will be tabulated: CR, PR, SD, PD and not evaluable (NE). Overall Response Rate (ORR) is defined as the proportion of patients with observed complete response (CR) or partial response (PR) according to the RECIST v1.1 criteria. Clinical Benefit Rate (CBR) is defined as the proportion of patients with CR, PR or SD x 6 months according to the RECIST v1.1 criteria. For ORR and CBR, patients without a post-baseline tumor assessment will be classed as not evaluable (NE) and considered as non-responder.

	For ORR and CBR, the estimates and the associated 95% CI (based on both asymptotic normal approximation and exact binomial methods) will be calculated.
1.3.2 Randomization	
Randomization Type:	☒ Open-Label ☐ Single Blind ☐ Double-Blind
1.4 Timing of Analysis	
Planned Interim Analysis	☐ Cohort Review / Dose Escalation ☒ Safety Review ☐ Interim Efficacy/Safety Analysis ☐ Independent DMC/DSMB ☐ Annual Report / Investigator Brochure (IB) ☐ Abstract / Scientific Presentation (Oral/Poster)
Final Analysis	The final analysis will occur when 42 patients have discontinued treatment, progressed, died or are still on treatment but have at least 12 months of follow-up (time from first treatment until last tumor assessment).
1.5 Responsibilities	
Trial Statistician:	Prepare SAP check list and TFL shells Review deliverables produced by Statistical Programmer
PK Statistician:	N/A
Independent Statistician:	N/A
1.6 Analysis Software	
Main statistical analysis:	SAS Version 9.3 or above
Other analysis software:	N/A
1.7 Coding	
☒ Adverse Events ☐ Medical History	☒ MedDRA: ☐ Version ☒ Most current release and update coding with new major releases ☒ NCI-CTCAE Version 4.03
☐ Concomitant Medication ☐ Prior Therapy ☐ Subsequent/Further Therapy	☐ WHO-Drug: ☐ Version ☐ Most current release and update coding with new major releases

2 Analysis Population	
Intent-To-Treat (ITT) Population definition:	☐ All patients who have started treatment in the study ☐ All patients who have been randomized in the study, regardless of whether they have received any treatment or not ☐ All patients who have been randomized and have started treatment in the study ☐ Other definition, specify:
Per Protocol (PP) Population to be used in analysis:	☐ Yes ☒ No If yes, please specify the criteria for exclusion from the PP population:
Safety (SAF) Population definition	☐ All patients who have started treatment in the study. Patients will be analyzed according to the actual treatment they have received. ☒ Other definition, specify: All patients who have received any dose of study treatment.
Other Analysis Population definition:	Efficacy Evaluable (EE): All patients who receive at least 1 cycle of study treatment and have at least one post-baseline assessment. (Patients who discontinue treatment during Cycle 1 will not be replaced in the study.)
3 Baseline Value Definitions	
	Last value prior to first date of study treatment
4 Efficacy	
Response Criteria Used:	☐ RECIST 1.0 ☒ RECIST 1.1 ☐ Cheson 2007 ☐ Modified RECIST – specify: ☐ Other criteria, Specify:
Efficacy Assessment Timepoints:	**Response Assessment Every 2 Cycles** Patients will be reevaluated for response to treatment after every 2 cycles of treatment, prior to the start of odd-numbered cycles. **End of Study Treatment**. The follow-up evaluations required after treatment ends (due to disease progression, or once the patient is discontinued due to unacceptable toxicity or decision to discontinue treatment by the patient or the study physician) are specified in Appendix D. **Follow-up for Patients Who Discontinue Prior to Disease Progression** Patients who discontinue study treatment prior to the occurrence of disease progression will be followed every 3 months (± 1 month) from the date of last dose of study drug until disease progression or for up to 3 years from the start of treatment whichever comes first. Assessments at these visits will be performed as described in Appendix D. **Survival Follow-up** After disease progression is documented, patients will be followed every 3 months (± 1 month) for survival (e.g., date and cause of death) for up to 3 years from the start of treatment or death whichever comes first.

Efficacy Endpoints:

	Endpoint	Primary Analysis Population	Other Analysis Population
Primary	PFS	Efficacy Evaluable	Safety
Secondary	OS, DOR,ORR, CBR	Efficacy Evaluable	Safety

Definition of Terms:

☒ Response

☒ Complete Response + Partial Response as best observed response

☐ Complete Response + Partial Response, confirmed with weeks apart.

☐ Other criteria, specify:

☒ Clinical Benefit

☐ Complete Response + Partial Response + Stable Disease as best observed response

☐ Complete Response + Partial Response (confirmed with weeks apart) + Stable Disease (at least weeks from start of treatment)

☒ Other criteria, specify: (Complete response (CR) + Partial response (PR) + Stable disease (SD) x 6 months)

☒ Progression

Disease progression (event) as defined by the RECIST v1.1 or death on study; non-protocol therapy (subsequent therapy) prior to incurring an event will be censored at the date of last tumor assessment prior to the start of subsequent therapy

☒ Subsequent Therapy

Non-protocol therapy prior to incurring an event

☐ Treatment Failure

N/A

Definition of Endpoints:

Start Date: ☐ Date of Randomization ☒ Date of First Treatment

End Date (*specify for all pertinent endpoints*):

Overall Survival: Event = Death

Situation	Date of Event or Censoring	Outcome
Death, while on-study or follow-up	Date of death	Event
Alive, as of end of study or follow-up	Date last known alive	Censored
Status unknown, as of end of study	Date last known alive	Censored

Progression-Free Survival: Event = Progression or Death

Situation	Date of Event or Censoring	Outcome
No baseline assessment	Date of first treatment	Censored
PD documented between scheduled visits, did not die, and received no subsequent therapy	First date of evaluated overall response = PD	Event
PD documented between scheduled visits, did not die, but received subsequent therapy prior to incurring progression event	Date of last evaluable tumor assessment prior to start of subsequent therapy	Censored

	Death while on-study without previous PD, and received no subsequent therapy	Date of death	Event
	Death while on-study and had previous PD, and received no subsequent therapy	First date of evaluated overall response = PD	Event
	Death while on-study without previous PD, but received subsequent therapy prior to death event	Date of last evaluable tumor assessment prior to start of subsequent therapy	Censored
	Death while on-study and had previous PD, but received subsequent therapy prior to PD event	Date of last evaluable tumor assessment prior to start of subsequent therapy	Censored
	No progression, no death	Date of last evaluable tumor assessment	Censored
	Treatment discontinuation for adverse event or other non-event reason	Date of last evaluable tumor assessment	Censored

☒ Overall Response Rate (ORR) ☐ Disease Control Rate (DCR) ☒ Clinical Benefit Rate (CBR) ☐ Early Progression Rate (EPR)	Default: Estimates of rates in each treatment arm ☐ Difference in rates & 95% confidence interval between treatment arms ☐ p-value, specify statistical test:
☐ Time To Progression (TTP) ☒ Progression-Free Survival (PFS) ☒ Overall Survival (OS) ☒ Duration of Response ☐ Duration of Stable Disease ☐ Time To Treatment Failure (TTF)	Default: Estimates of medians in each treatment arm ☒ Other quartiles or percentages of survival required, specify: PFS: @4 months and 6 months: percentages & 95% confidence intervals ☐ Hazard ratio & 95% confidence interval between treatment arms, unstratified ☐ p-value, specify statistical test: ☐ Hazard ratio & 95% confidence interval between treatment arms, stratified (specify stratification factor(s)): ☐ p-value, specify statistical test:
☒ Other, Specify:	Median Follow-up: Estimate of median, 25th and 7th quartiles; Follow-up point estimates: @ 4 months, 6 months, and 12 months: percentages & 95% confidence intervals
5 Safety	
Adverse Events	Definition of Treatment-Emergent Adverse Event (TEAE): Treatment-emergent AEs are those with an onset on or after the initiation of therapy
Laboratory Data	Data will be summarized by: ☐ NCI-CTCAE for CTCAE-gradable parameters, and H/L for non-CTCAE-Gradable parameter ☐ H/L for all lab parameters

Tier 1 Study – Tables, Figures & Listings

Standard TFLs			
Table No	**Description**	**Variables/Analyses To Be Included**	**Population**
Table 1	Patient Disposition	☐ Number of patients screened ☒ Number of patients enrolled ☒ Number of patients treated ☒ Reason for treatment discontinuation ☒ Reason for study discontinuation ☐ Other, specify:	Enrolled Patients
Table 2	Demographic Characteristics	☒ Age: N, Mean, SD, Median, Min, Max ☒ Age Group: <65, >=65 ☒ Sex ☒ Race ☒ Ethnicity ☒ ECOG ☐ Other, specify:	Enrolled Patients
Table 3	Disease History - General	☒ Histology ☒ Disease staging at initial diagnosis ☐ Time from initial diagnosis to first dose ☐ Number of patients with metastatic disease ☒ Sites of metastases ☒ Other, specify: Histology Grade	Enrolled Patients
Table 4	Prior Hormonal Therapy	Time [months] from last hormonal therapy to first date of study treatment: N, Mean, SD, Median, Min, Max	Safety
Table 5	Treatment and Dose Modifications	Duration on Treatment (weeks), N, Mean, SD, Median, Min, Max Dose Reduction (n, %) None Patients with 1 Patients with 2 Patients with >= 3 Dose Interruption (n, %) None Patients with 1 Patients with 2 Patients with >= 3	Safety
Table 6	Measurable Lesions	Measurable Lesions (n, %) Non-Measurable Lesions (n, %) Evaluable Bone Only Disease (n, %)	Enrolled Patients
Table 7	Best Overall Response	Best overall response (n, %): Complete response (CR), Partial response (PR), Stable disease (SD), NonCR/NonPD, Progressive disease (PD), Not evaluable (NE), Not applicable (N/A) Missing Objective Response Rate (ORR) (= CR+PR): ORR, 95% Confidence interval Clopper-Pearson	Efficacy Evaluable, Safety

Standard TFLs			
Table No	**Description**	**Variables/Analyses To Be Included**	**Population**
		Normal Approximation Clinical Benefit Rate (CBR) (=CR+PR+SD>=4months): CBR, 95% Confidence interval Clopper-Pearson Normal Approximation Clinical Benefit Rate (CBR) (=CR+PR+SD>=6months): CBR, 95% Confidence interval Clopper-Pearson Normal Approximation]	
Table 8	Progression-free Survival (Kaplan-Meier estimates & 95% CI)	Number of patients with events, Number of patients censored, Median Progression-free Survival [months (95% CI)] 25% Percentile Follow-up [months (95% CI)] 75% Percentile Follow-up [months (95% CI)] Progression-free Survival Estimates [probability, (95% CI)]: 4 months, 6 months, 12 months	Efficacy Evaluable, Safety
Table 9	Overall Survival (Kaplan-Meier estimates & 95% CI)	Number of patients with events, Number of patients censored, Median Overall Survival [months (95% CI)] 25% Percentile Follow-up [months (95% CI)] 75% Percentile Follow-up [months (95% CI)] Overall Survival Estimates [probability, (95% CI)]: 4 months, 6 months, 12 months	Efficacy Evaluable, Safety
Table 10	Adverse Event Overview	Any Adverse Event Treatment-related Adverse Event Everolimus-related Adverse Event Anti-Estrogen Therapy-related Adverse Event Serious Adverse Event Treatment-related Serious Adverse Event Serious Adverse Event leading to Death Treatment-related Serious Adverse Event leading to Death Adverse Events leading to Treatment Discontinuation Adverse Events leading to Treatment Interruption Adverse Events leading to Treatment Reduced	Safety

Standard TFLs			
Table No	**Description**	**Variables/Analyses To Be Included**	**Population**
Table 11	Any Treatment-Emergent Adverse Event by System Organ Class and Preferred Term	System organ class, Preferred term, CTCAE grade [all statistics: (n, %)]	Safety
Table 12	Any Treatment Related-Emergent Adverse Event by System Organ Class and Preferred Term	System organ class, Preferred term, CTCAE grade [all statistics: (n, %)]	Safety
Table 13	Any Treatment Related-Emergent Adverse Event by SCRI Grouped Adverse Event Term	SCRI grouped AE term, CTCAE grade [all statistics: (n, %)]	Safety
Table 14	Treatment Serious-Emergent Adverse Event by System Organ Class and Preferred Term	System organ class, Preferred term, CTCAE grade [all statistics: (n, %)]	Safety
Table 15	Treatment Related and Serious-Emergent Adverse Event by System Organ Class and Preferred Term	System organ class, Preferred term, CTCAE grade [all statistics: (n, %)]	Safety
Table 16	Duration of Response (DOR) (Kaplan-Meier estimates & 95% CI)	Number of patients with events, Number of patients censored, Duration of Response: Median [months (95% CI)] Duration of Response Estimates [probability, (95% CI)]: 4 months, 6 months	Efficacy Evaluable, Safety
Table 17	Median Follow-up (Kaplan-Meier estimates & 95% CI)	Number of patients with events, Number of patients censored, Median Follow-up [months (95% CI)] 25% Percentile Follow-up [months (95% CI)] 75% Percentile Follow-up [months (95% CI)] Follow-up Estimates [probability, (95% CI)]: 4 months, 6 months, 12 months	Efficacy Evaluable
Table 18	Genetic Abnormalities	Patients with: Any abnormality (n, %) Abnormality in PI3K/Akt/mTOR pathway (n, %) ESR1 abnormality (n, %)	Safety

Figure No	Description	Variables/Analyses To Be Included	Population
Figure 1	Overall Survival	Timescale to be used on horizontal axis: ☐ Day ☐ Week ☒ Month ☐ Year	Efficacy Evaluable, Safety
Figure 2	Progression-free Survival	Timescale to be used on horizontal axis: ☐ Day ☐ Week ☒ Month ☐ Year	Efficacy Evaluable, Safety

Listing No.	Title	Variables/Analyses To Be Included	Population
1	Prior Systemic Therapy	Patient Number Start Date End Date Medication Taken Regimen Number Disease Setting Best Overall Response Reason Therapy Ended - Specify	Enrolled Patients
2	Current Hormonal Therapy	Patient Number Visit Name Disease Setting Medication Taken Start Date End Date Reason for Therapy End	Enrolled Patients
3	Biodesix Information	Patient Number Age Sex Race Ethnicity Performance Status at Screening (ECOG) ER (most recent) PR HER 2 Current Endocrine Therapies Prior Endocrine Therapies Prior Adjuvant Therapies Prior Metastatic Therapies Prior Neoadjuvant Therapies Disease Stage at Diagnosis Date of Treatment Start Best Overall Response Date of Best Overall Response PFS (months) OS (months)	Enrolled Patients
4	Patients with ESR1 Mutation	Patient Number	Safety, whose Tissue Samples were Assessed