Master Statistical Analysis Plan Checklist

for Investigator Initiated Trials

Phase II Trial of Eribulin in Patients Who Do Not Achieve Pathologic Complete Response (pCR) Following Neoadjuvant Chemotherapy

Sponsor:	**Sarah Cannon Development Innovations (Innovations)**
Study Drug:	**ERIBULIN**
Protocol Number:	**BRE 186**
Prepared By:	**Innovations**

Statistical Analysis Plan Checklist for Investigator Initiated Trials

History of Changes

This document has undergone the following changes:

Version Number	Version Date	Description of Changes
1.0	03APR2018	Original document

Statistical Analysis Plan Checklist Review and Approval

Approved By:

Innovations Biostatistician David Moorman	Date
Innovations Managerial Peer-Reviewer	Date
Innovations Tier 1 Manager	Date
Innovations Study Chair	Date

1.1 Objectives	
Primary Objective:	Assess the efficacy of eribulin when administered to patients who do not achieve pCR following standard neoadjuvant chemotherapy (+/- trastuzumab). The primary endpoint will be 2-year disease-free survival (DFS) rate.
Secondary Objectives:	Assess the feasibility of administering 6 cycles of eribulin following standard neoadjuvant chemotherapy and primary surgical therapy. Assess the toxicity of eribulin in this patient population.
1.2 Study Design	
Study Type	☒ Non-Randomized ☐ Randomized (Allocation Ratio:)
Details	This is a nonrandomized, open-label trial that will evaluate 6 cycles of eribulin administered postoperatively in patients who do not achieve pCR following a standard neoadjuvant chemotherapy regimen. There will be three cohorts of patients based on tumor type: triple-negative (A), hormone-receptor-positive/HER2-negative (B), and HER2-positive (C). Patients who are HER2-positive will receive trastuzumab as part of neoadjuvant treatment and concurrently with postoperative eribulin treatment. The trial population will consist of consenting female patients who do not achieve pCR (i.e., have residual invasive disease in breast or lymph node tissue) after treatment with a standard neoadjuvant chemotherapy regimen and surgery. One-hundred forty-eight patients will be enrolled in this trial (54 in Cohort A, 42 in Cohort B, and 52 in Cohort C). All patients will receive eribulin 1.4 mg/m2 IV Days 1 and 8 every 21 days for 6 cycles. Patients with HER2-positive tumors will also receive trastuzumab 6 mg/kg IV Day 1 every 21 days to complete a total of 1 year (52 weeks) of treatment from the start of neoadjuvant administration. If the last dose of trastuzumab was given >28 days from trial treatment start, the loading dose should be 8 mg/kg. Patients will receive either eribulin alone (Cohorts A & B) or eribulin + trastuzumab (Cohort C) based on their HER2 status and/or hormone receptor status.

Cohort	**Trial Drugs & Mode of Administration**
Cohort A: Triple-negative	Eribulin 1.4 mg/m^2 IV (Days 1 & 8 every 21 days)
Cohort B: Hormone-receptor-positive/HER2-negative	Eribulin 1.4 mg/m^2 IV (Days 1 & 8 every 21 days)
Cohort C: HER2-positive	Eribulin: 1.4 mg/m^2 IV (Days 1 & 8 every 21 days) Trastuzumab: 6 mg/kg IV (Day 1 every 21 days)

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 following the completion of the trial.
1.5 Responsibilities	
Trial Statistician:	Prepare SAP checklist and TFL shells. Review deliverables produced by statistical programmers.
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
3 Analysis Set	
Response Evaluable Analysis Set 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) Analysis Set to be used in analysis:	☐ Yes ☒ No If yes, please specify the criteria for exclusion from the PP population:
Safety (SAF) Analysis Set 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:
Other Analysis Set definition:	Note: Cohorts for TFLs will be: Cohort A: Triple-negative Cohort B: Hormone-receptor-positive/HER2-negative Cohort C: HER2-positive
4 Baseline Value Definitions	
	Last value prior to first study drug treatment.
5/6 Efficacy	
Response Criteria Used:	☐ RECIST 1.0 ☐ RECIST 1.1 ☐ Cheson 2007 ☐ Modified RECIST – specify: ☐ Other criteria, Specify: Complete staging work-up to confirm localized disease should include computed tomography (CT) scans of the chest and abdomen/pelvis (abdomen/pelvis preferred; abdomen accepted), a CT scan of the head or MRI of the brain (if symptomatic), and either a positron emission tomography (PET) scan or a bone scan. (Note: a PET/CT is acceptable for baseline imaging in lieu of CT examinations or bone scan). Negative scans performed prior to the initiation of neoadjuvant therapy, or at any subsequent time, are acceptable and do not need to be repeated.

Efficacy Assessment Timepoints:	Patients will be followed every 3 months during years 1 and 2 for toxicity and disease progression.

Efficacy Endpoints:

	Endpoint	Primary Analysis Population	Other Analysis Population
Primary	Disease-Free Survival (DFS)	Response Evaluable Analysis Set	
Secondary	NA		

Definition of Terms:

☐ Response

☐ Complete Response + Partial 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:

☒ Progression

As reported by investigator

☐ Subsequent Therapy

☐ Treatment Failure

☒ Duration of Follow-up

Defined as time from first treatment to death or date last known alive, reported in months

Definition of Endpoints:

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

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

Disease-Free Survival: Event = Progression or Death

Situation	Date of Event or Censoring	Outcome
No baseline assessment	Date of first treatment	Censored
Progression documented	Date of progression	Event
Death	Date of death	Event
No progression or death	Date last known alive	Censored
Initiation of non-protocol anticancer therapy	Date of subsequent therapy	Censored
No progression, death, or subsequent therapy	Date last known alive	Censored

☐ Overall Response Rate (ORR)	Default: Estimates of rates in each treatment arm ☐ Rate & 95% confidence interval (both asymptotic normal approximation and exact binomial) ☐ p-value, specify statistical test:
☐ Disease Control Rate (DCR)	
☐ Clinical Benefit Rate (CBR)	
☐ Early Progression Rate (EPR)	
☐ Time To Progression (TTP)	Default: Estimates of medians (DFS) ☒ Other quartiles or percentages of survival required, specify: DFS estimation in 6-month increments ☐ 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:
☒ Disease-Free Survival (DFS)	
☐ Overall Survival (OS)	
☐ Duration of Response	
☐ Duration of Stable Disease	
☐ Time To Treatment Failure (TTF)	
☐ Other, Specify:	
7 Safety	
Adverse Events	Definition of Treatment-Emergent Adverse Event (TEAE): any adverse event (AE) that starts or worsens after the start of the first dose of study treatment up to 30 days post last dose. Frequency and severity of AEs. Worst grade per patient for select AEs: related AEs by maximum grade by cohort
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 Worst grade per patient for select labs

Tier 1 Study – Tables, Figures & Listings

Standard TFLs			
Table No	**Description**	**Variables/Analyses To Be Included**	**Analysis Set**
Table 1	Disease-free Survival	Kaplan-Meier Number of patients with events, Number of patients censored, Median disease-free survival [months (95% CI)] Probability of events at: 6 month increments	Response Evaluable Analysis Set

Standard TFLs			
Table No	**Description**	**Variables/Analyses To Be Included**	**Analysis Set**
Table 2	Duration of Follow-up	Continuous numeric: N Mean Standard deviation Median Minimum Maximum	Safety Analysis Set
Table 3	Treatment-related Adverse Events by Maximum Reported CTCAE Grade	by Maximum CTCAE Grade, per Cohort	Safety Analysis Set

Figure No	Description	Variables/Analyses To Be Included	Analysis Set
Figure 1a	Disease-Free Survival – Cohort A	Timescale to be used on horizontal axis: ☐ Day ☐ Week ☒ Month ☐ Year	Response Evaluable Analysis Set
Figure 1b	Disease-Free Survival – Cohort B	Timescale to be used on horizontal axis: ☐ Day ☐ Week ☒ Month ☐ Year	Response Evaluable Analysis Set
Figure 1c	Disease-Free Survival – Cohort C	Timescale to be used on horizontal axis: ☐ Day ☐ Week ☒ Month ☐ Year	Response Evaluable Analysis Set

Listing No.	Title	Variables/Analyses To Be Included	Analysis Set