Master Statistical Analysis Plan Checklist

for Investigator Initiated Trials

A Two Arm Safety Study of Regorafenib before or after SIR-Spheres® Microspheres (90Y) for the Treatment of Patients with Refractory Metastatic Colorectal Cancer and Liver Metastases

Sponsor:	**Sarah Cannon Development Innovations (Innovations)**
Study Drug:	**SIR-Spheres® Microspheres**
Protocol Number:	**GI 189**
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	22MAY2018	Original document

1.1 Objectives	
Primary Objective:	To evaluate the safety of two treatment cohorts combining regorafenib and SIR-Spheres microspheres (SIR-Spheres) radioemoblization in patients with refractory metastatic colorectal cancer (mCRC) with liver metastasis.
Secondary Objectives:	To evaluate the overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) of patients with refractory mCRC when treated with combination SIR-Spheres and regorafenib in the two sequencing cohorts.
1.2 Study Design	
Study Type	☒ Non-Randomized ☐ Randomized (Allocation Ratio:)
Details	This is an open-label study comparing the safety of two treatment cohorts in which radioembolization will be administered using the device SIR-Spheres microspheres (90Y resin microspheres) in combination with regorafenib to patients with mCRC with liver metastases. The two treatment cohorts will be evaluated for safety, ORR, PFS, and OS. Twenty-five patients will be treated in each cohort. The first cohort will complete enrollment before the second cohort opens. There will be no randomization or blinding. Blood samples will be collected from all patients prior to the hepatic angiogram and 99mTc MAA lung shunt scan, on Day 8 after SIR-Spheres treatment, and Day 30 (pre-dose) after SIR-Spheres treatment (see Section 5.1). Expressions of cytokines and proteins will be measured to explore potential biomarkers that may correlate with clinical outcome.
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	6 months after last patient has been recruited into study
1.5 Responsibilities	
Trial Statistician:	Development of SAP and shells Review deliverables presented 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:	None

1.7 Coding	
☒ Adverse Events ☐ Medical History	☒ MedDRA: ☐ Version ☒ Most current release and update coding with new major releases ☐ NCI-CTCAE Version
☒ Concomitant Medication ☐ Prior Therapy ☐ Subsequent/Further Therapy	☒ WHO-Drug: ☐ Version ☒ Most current release and update coding with new major releases
3 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:
Other Analysis Population definition:	N/A
4 Baseline Value Definitions	
	Last value prior to first date of study drug treatment
5/6 Efficacy	
Response Criteria Used:	☐ RECIST 1.0 ☒ RECIST 1.1 ☐ Cheson 2007 ☐ Modified RECIST – specify: ☐ Other criteria, Specify:

Efficacy Assessment Timepoints:	Assessed during treatment at week 6 and week 12. Patients continuing treatment after week 12 will be assessed at 8 week intervals. Patients with progressive disease (PD), unacceptable toxicity, or who withdraw consent will be removed from the study. Patients will be assessed at end of treatment visit During follow-up, patients will be assessed every 3 months up to 6 months.

Efficacy Endpoints:

	Endpoint	Primary Analysis Population	Other Analysis Population
Primary	Overall Response Rate (ORR)	ITT Population	
Secondary	Progression-Free Survival (PFS) Overall Survival (OS)	ITT Population	

Definition of Terms:

☒ Response

- ☐ Complete Response + Partial Response as best observed response
- ☒ Complete Response + Partial Response, confirmed with 4 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 defined in Appendix C of the protocol.

☐ Subsequent Therapy

☐ Treatment Failure

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	Date of death	Event
Alive on date of data cutoff	Date last known alive	Censored
Alive before date of data cutoff, but status unknown on date of data cutoff (e.g. lost to follow-up)	Date last known alive	Censored

<table>
<tr><td></td><td>Progression-Free Survival: Event = Progression or Death
<table>
<tr><th>Situation</th><th>Date of Event or Censoring</th><th>Outcome</th></tr>
<tr><td>No baseline assessment</td><td>Date of first treatment</td><td>Censored</td></tr>
<tr><td>Progression documented between scheduled visits</td><td>First date of evaluated overall response = PD</td><td>Event</td></tr>
<tr><td>No progression</td><td>Date of last evaluable tumor assessment</td><td>Censored</td></tr>
<tr><td>Treatment discontinuation for adverse event or other reason</td><td>Date of last evaluable tumor assessment</td><td>Censored</td></tr>
<tr><td>Death before first PD assessment</td><td>Date of death</td><td>Event</td></tr>
<tr><td>Death before the next scheduled tumor assessment</td><td>Date of death</td><td>Event</td></tr>
<tr><td>Death after one missed tumor assessment but before second missed tumor assessment</td><td>Date of death</td><td>Event</td></tr>
<tr><td>Death after two or more missed tumor assessment</td><td>Date of last evaluable tumor assessment</td><td>Censored</td></tr>
</table></td></tr>
<tr><td>☒ Overall Response Rate (ORR)
☐ Disease Control Rate (DCR)
☐ Clinical Benefit Rate (CBR)
☐ Early Progression Rate (EPR)</td><td>Default: Estimates of rates in each treatment arm
☒ Difference in rates & 95% confidence interval between treatment arms
☐ p-value, specify statistical test:</td></tr>
<tr><td>☐ Time To Progression (TTP)
☒ Progression-Free Survival (PFS)
☒ Overall Survival (OS)
☐ Duration of Response
☐ Duration of Stable Disease
☐ Time To Treatment Failure (TTF)</td><td>Default: Estimates of medians in each treatment arm
☒ Other quartiles or percentages of survival required, specify: probability evaluated at 6 month 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:</td></tr>
<tr><td>☐ Other, Specify:</td><td></td></tr>
<tr><td>7 Safety</td><td></td></tr>
<tr><td>Adverse Events</td><td>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.</td></tr>
<tr><td>Laboratory Data</td><td>Data will be summarized by:
☒ NCI-CTCAE for CTCAE-gradable parameters, and H/L for non-CTCAE-Gradable parameter</td></tr>
</table>

	☐ H/L for all lab parameters

Tier 1 Study – Tables, Figures & Listings

Standard TFLs			
Table No	**Description**	**Variables/Analyses To Be Included**	**Subgroup Analyses**
Table 1	Summary of Demographics and Disease Characteristics	☒ Age: Median, Min, Max ☐ Age Group: ☒ Sex ☒ Race ☒ ECOG ☒ Other, specify: Primary diagnosis, KRAS, BRAF	Safety Analysis Set
Table 2	Summary of Metastatic Involvement at study entry	☐ Histology ☐ Disease Staging ☐ Time from Diagnosis ☒ Other, specify: sites of metastatic involvement (count and percent of patients per involved site)	Safety Analysis Set
Table 3	Summary of Regorafenib Exposure and Treatment Modifications	Treatment duration, number of patients with each treatment modification, reasons for dose modifications	Safety Analysis Set
Table 4	Summary of SIR-Spheres Exposure	Activity delivered to liver (mCi), lung shunt fraction, total tumor volume (mL): number of patients, Mean, SD, Median, Min, Max Treatment planning (left, right, whole): number and percent of patients	Safety Analysis Set
Table 4	Summary of Treatment Discontinuations	Number of patients with treatment discontinuation, reasons for treatment discontinuation	Safety Analysis Set
Table 5	Summary of Best Overall Response	Best overall response: Complete response (CR), Partial response (PR), Stable disease (SD), progressive disease (PD), not evaluable (NE) Objective response rate (ORR) (CR + PR): ORR, 95% Confidence interval CR and PR confirmed	ITT Population/Efficacy Analysis Set
Table 6	Summary of Progression-Free Survival	Kaplan-Meier Number of patients with events, Number of patients censored, Median, 25th and 75th percentiles for progression free survival [months (95% CI)] Probability of events evaluated in 6 month intervals	ITT Population/Efficacy Analysis Set
Table 7	Summary of Overall Survival	Kaplan-Meier	ITT Population/Efficacy Analysis Set

Standard TFLs			
Table No	**Description**	**Variables/Analyses To Be Included**	**Subgroup Analyses**
		Number of patients with events, Number of patients censored, Median, 25th and 75th percentiles for overall survival [months (95% CI)] Probability of events evaluated in 6 month intervals	
Table 8	Summary of Treatment-Related Adverse Events	Sarah Cannon/Modified CTCAE coding By CTCAE grade	Safety Analysis Set

Figure No	Description	Variables/Analyses To Be Included	Subgroup Analyses
Figure 1	Progression-Free Survival	Timescale to be used on horizontal axis: ☐ Day ☐ Week ☒ Month ☐ Year	ITT Population/Efficacy Analysis Set
Figure 2	Overall Survival	Timescale to be used on horizontal axis: ☐ Day ☐ Week ☒ Month ☐ Year	ITT Population/Efficacy Analysis Set