SCRI DEVELOPMENT INNOVATIONS

Statistical Analysis Plan Checklist

for Investigator Initiated Trials

Open-Label Study to Determine the Feasibility of MLN9708 as Maintenance after Allogeneic Stem Cell Transplant for Multiple Myeloma, Followed by an Expansion Phase at the Maximum-Tolerated Dose (MTD)

Sponsor:	**Sarah Cannon Development Innovations (Innovations)**
Study Drug:	**MLN9708**
SCRI Protocol Number:	**MM 42**
Prepared By:	**Innovations**

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History of Changes

This document has undergone the following changes:

Version Number	Version Date	Description of Changes
1.0	06 JAN 2020	Original document

Statistical Analysis Plan Checklist Review and Approval

Approved By:

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

1.1 Objectives	
Primary Objective:	Safety of MLN9708 when used as maintenance after allogeneic stem cell transplant for multiple myeloma
Secondary Objectives:	Maximum-tolerated dose (MTD) of MLN9708 in this patient population Progression-free survival (PFS) at 2 years after initiation of maintenance therapy Overall survival (OS) at 2 years after allogeneic stem cell transplant Incidence of graft-versus-host disease (GVHD) in patients receiving allogeneic stem cell transplant and maintenance with MLN9708 Effect of MLN9708 on immune effector cells after allogeneic stem cell transplant
1.2 Study Design	
Study Type	☒ Non-Randomized ☐ Randomized (Allocation Ratio:)
Details	This is a Phase II, open-label, multicenter, non-randomized study to determine the feasibility of MLN9708 as maintenance after allogeneic stem cell transplant for multiple myeloma. Patients will be enrolled between Days 45 and 120 after allogeneic transplant and will receive MLN9708 on Days 1, 8, and 15 of each 28-day cycle for 6 cycles. Up to 18 patients will be enrolled in the dose-escalation phase to define the MTD of MLN9708. An additional 20 patients will be enrolled in the expansion phase at the MTD. PFS is defined as the time from the first day of study drug administration (Day 1) to disease progression as defined by the International Myeloma Working Group Uniform Response Criteria (see Appendix E of protocol), or death on study. Patients who are alive and free from disease progression will be censored at the date of last tumor assessment. OS is defined as the time from the first day of study drug administration (Day 1) to death on study. Patients who are alive will be censored at the date of last known date alive. PFS and OS (efficacy secondary endpoints) estimates will be generated using Kaplan-Meier methods, both for all patients enrolled and those patients receiving the MTD. Two-year PFS and OS estimates with 95% confidence intervals (CIs), and median PFS and OS with 95% CIs, will be generated and reported accordingly.
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	As determined by the Study Chair in consultation with the clinical team

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 v4.0
☐ 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	☒ The Safety population will consist of all patients who received at least one dose of MLN9708. ☐ Other definition, specify:
Other Analysis Population definition:	The Efficacy Evaluable population will consist of all patients with measurable or evaluable disease at baseline who receive at least 1 dose of MLN9708 and undergo at least one post-baseline disease assessment. In addition, patients who discontinued the study prior to their first post-baseline disease assessment due to death or progressive disease will also be included in the Efficacy Evaluable population.
4 Baseline Value Definitions	
	Information collected and procedures performed for each patient at ≤7 days prior to initiation of treatment.
5/6 Efficacy	
Response Criteria Used:	☐ RECIST 1.0 ☐ RECIST 1.1 ☐ Cheson 2007 ☐ Modified RECIST – specify: ☒ Other criteria, Specify: International Myeloma Working Group Uniform Response Criteria
Efficacy Assessment Timepoints:	Patients will be re-evaluated for response to treatment after 2 cycles of treatment. Response will be assessed at 8-week intervals (±1 week) during study treatment. Patients with progressive disease (PD) or unacceptable toxicity should be discontinued from the study; patients with stable disease (SD) or response to therapy will continue treatment through 6 cycles.

Efficacy Endpoints:

	Endpoint	Primary Analysis Population	Other Analysis Population
Primary	PFS	Efficacy Evaluable	
Secondary	OS	Efficacy Evaluable	

Definition of Terms:

☒ Response

☐ Complete Response + Partial Response as best observed response

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

☒ Other criteria, specify:
International Myeloma Working Group Uniform Response Criteria:

sCR (stringent complete response) **CR** (complete response)
VGPR (very good partial response) **PR** (partial response)
SD (stable disease) **PD** (progressive disease)

☐ 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

Definition of Endpoints:

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

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

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

	<table><tr><td>Death while on-study without previous PD, but received subsequent therapy prior to death event</td><td>Date of last evaluable tumor assessment prior to start of subsequent therapy</td><td>Censored</td></tr><tr><td>Death while on-study and had previous PD, but received subsequent therapy prior to PD event</td><td>Date of last evaluable tumor assessment prior to start of subsequent therapy</td><td>Censored</td></tr><tr><td>No progression, no death</td><td>Date of last evaluable tumor assessment</td><td>Censored</td></tr><tr><td>Treatment discontinuation for adverse event or other non-event reason</td><td>Date of last evaluable tumor assessment</td><td>Censored</td></tr></table> **Overall Survival: Event = Death** <table><tr><th>Situation</th><th>Date of Event or Censoring</th><th>Outcome</th></tr><tr><td>Death, while on-study or follow-up</td><td>Date of death</td><td>Event</td></tr><tr><td>Alive, as of end of study or follow-up</td><td>Date last known alive</td><td>Censored</td></tr><tr><td>Status unknown, as of end of study</td><td>Date last known alive</td><td>Censored</td></tr></table>
☐ 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, OS: 2 year PFS and OS with 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:	
7 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, and will be graded according to NCI CTCAE v4.0.
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**	**Subgroup Analyses**
Table 1	Summary of Patient Disposition	☐ Number of patients screened ☐ Number of patients randomized ☒ Number of patients treated ☒ Reason for treatment discontinuation ☐ Reason for study withdrawals ☒ Other, specify: Patient Deaths; Time on Study	
Table 2	Summary of Demographic Characteristics	☒ Age: Mean, SD, Median, Min, Max ☐ Age Group: ☒ Sex ☒ Race ☒ ECOG ☐ Other, specify:	
Table 3	Summary of Disease History	☒ Histology ☒ Disease Staging ☐ Time from Diagnosis ☐ Other, specify: Baseline FISH Baseline Cytogenetics	
Table 4	Summary of Patient Treatment and Dose Modifications (*reductions, interruptions*)		
Table 5	Summary of Grade 3+ Adverse Events		
Table 6	Summary of Treatment-Related Grade 3+ Adverse Events		
Table 7	Summary of Serious Adverse Events		
Table 8	Summary of Treatment-Related Serious Adverse Events		
Table 9	Summary of Treatment Related Adverse Events Leading to Death		
Table 10	Summary of Best Overall Response		
Table 11	Summary of Response Over Time		
Table 12	Summary of Progression-Free Survival (*Kaplan-Meier estimates & 95 CI*)		
Table 13	Summary of Overall Survival (*Kaplan-Meier estimates & 95 CI*)		
Table 14	Summary of Adverse Events with >= 5% Frequency (*for: CTGOV*)		

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	
Figure 2	Overall Survival	Timescale to be used on horizontal axis: ☐ Day ☐ Week ☒ Month ☐ Year	

Listing No.	Title	Variables/Analyses To Be Included	Subgroup Analyses