Protocol Title: A Multicenter Phase 1b Randomized, Placebo-controlled, Blinded Study to Evaluate the Safety, Tolerability and Efficacy of Microbiome Study Intervention Administration in Combination with Anti-PD-1 Therapy in Adult Patients with Unresectable or Metastatic Melanoma

Protocol Number: PICI0014

Amendment Number: Not applicable

Compound Number: Microbiome Study Intervention (Oral fecal microbiota transplant [FMT] or SER-401) and Anti-PD-1 Monoclonal Antibody (Nivolumab)

Short Title: **M**elanoma **C**heckpoint and **G**ut Mic**r**obiome **A**lteration **w**ith Microbiome Intervention (MCGRAW)

Sponsor Name and Legal Registered Address:

Parker Institute for Cancer Immunotherapy
1 Letterman Drive
Suite D3500
San Francisco, CA 94129

Tel: 415-985-7311

Fax: 415-872-5305

Regulatory Agency Identifying Number(s):

IND NUMBER: 018517

EudraCT NUMBER: Not applicable

Approval Date: Final Protocol: 25 Sep 2018

Amendment 1: 14 Nov 2018

Amendment 2: 08 Jan 2020

SPONSOR APPROVAL PAGE

Date: 08JAN2020

Ramy Ibrahim, MD
Vice President, Clinical Development

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by Parker Institute for Cancer Immunotherapy.
- Not to implement any changes to the protocol without written agreement from Parker Institute for Cancer Immunotherapy and prior review and written approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) except where necessary to eliminate an immediate hazard to patients.
- That I am thoroughly familiar with the appropriate use of the study drug(s), as described in this protocol and any other information provided by Parker Institute for Cancer Immunotherapy including, but not limited to, the current Investigator's Brochure(s).
- That I am aware of, and will comply with, the International Conference on Harmonisation for Good Clinical Practices (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the study drugs, the Parker Institute for Cancer Immunotherapy study protocol, and of their study-related duties and functions as described in the protocol.
- That I agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the Parker Institute for Cancer Immunotherapy or for a partnership in which the Parker Institute for Cancer Immunotherapy is involved, and that I will immediately disclose in writing to the Parker Institute for Cancer Immunotherapy if any person who is involved in the study is debarred, or if any proceeding for debarment is pending.

Signature: _____ Date: _____

Name (print): _____

Principal Investigator

Site Number: _____

Amendment 1: 14 Nov 2018

Text revisions resulting from this amendment are incorporated in the synopsis and body of Protocol Amendment 1. Major changes to the protocol are summarized below.

Key Revisions in Amendment 1

Section # and Name	Description of Change
Safety Assessments	
8.3.1 Time Period and Frequency for Collecting AE, AESI, SAE, and Other Reportable Safety Event Information	Clarified that all SAEs and AEs, including AESIs, will be collected until 90 days after the last dose of nivolumab (ie, removed the following text: "or until the initiation of a new systemic anticancer therapy, whichever occurs first.").
8.3.4 Regulatory Reporting Requirements for SAEs	Added text to address safety reporting to drug manufacturers.
10.5.3 Recording AEs and SAEs	Updated the definitions for toxicity attribution for AEs, AESIs, and SAEs
Study Design	
4.1 Overall Design	Added text to reflect that the first 5 participants in each microbiome study intervention group (ie, FMT/matching placebo or SER-401/matching placebo) will be contacted twice following the first dose of nivolumab (once between Days 2-4 and once on Day 7 [± 1 day to accommodate weekends or holidays]) to assess for emerging AEs that may require early intervention.
Study Intervention	
Synopsis	Added text to reflect staggering administration of study intervention by at least 1 day for the first 5 participants enrolled in each microbiome study group (ie, FMT/matching placebo or SER-401/matching placebo) to monitor for safety.
6.1 Study Interventions Administered	Added text to reflect staggering administration of study intervention by at least 1 day for the first 5 participants enrolled in each microbiome study group (ie, FMT/matching placebo or SER-401/matching placebo) to monitor for safety.
6.6.1 Dose Modifications with Nivolumab and Oral Microbiome Study Intervention	Added new criterion to Table 4 for any infection with an organism acquired from FMT or SER-401.
7.1.1 Study-wide Hold for Specified Safety Events	Added new section to reflect that occurrence of any report of an SAE related to FMT or SER-401 or of any infection with an organism acquired from FMT or SER-401 will result in a study-wide hold and immediate discontinuation of oral microbiome study intervention administration.
Study Assessments and Procedures	
1.3 Schedule of Activities	Revised Table 1 as follows: • changed window for Cycle 1, Day 1 to ±1 day and the window for the Q3M follow up visits to ±14 days; • clarified the timing of the baseline disease assessment and revised text to describe disease assessment schedule during treatment phase and follow-up to reflect schedule of every 12 weeks until radiographic PD or the start of subsequent therapy;

Section # and Name	Description of Change
	• revised AE collection schedule to reflect continuous nature of this activity and added text to reflect that the first 5 participants in each microbiome study intervention group (ie, FMT/matching placebo or SER-401/matching placebo) will be contacted twice during Cycle 1 (once between Days 2-4 and once on Day 7 [± 1 day to accommodate weekends or holidays]) to assess for emerging AEs that may require early intervention
Statistical Considerations	
9.5.1 Data Monitoring Committee	Added to text to reflect that it is the responsibility of the Data Monitoring Committee (DMC) to adjudicate study-holding criteria per the study-specific DMC charter.
Clarification of Document	
General Revisions	Document updated to address minor typographical errors and editorial changes for clarity.
Investigator Protocol Agreement Page	Revised as follows: • added reference to International Conference on Harmonisation with regard to Good Clinical Practices; • added bullet addressing requirement to exclude persons who have been debarred from conducting or working on clinical studies.
7.1.1 Temporary Discontinuation	Removed section as it was not applicable to this protocol.

Amendment 2: 08 Jan 2020

Text revisions resulting from this amendment are incorporated in the synopsis and body of Protocol Amendment 2. Major changes to the protocol are summarized below.

Key Revisions in Amendment 2

Section # and Name	Description of Change
Safety Assessments	
1.3 Schedule of Activities 4.1 Overall Design 6.5 Concomitant Therapy 8.3.1 Time Period and Frequency for Collecting AE, AESI, SAE, and Other Reportable Safety Event Information 8.3.2 Follow-up Event Reporting	Clarified that all adverse events, adverse events of special interest, serious adverse events, and concomitant therapies, will now be collected for at least 100 days after the last dose of study intervention, instead of at least 90 days.
1.3 Schedule of Activities 4.1 Overall Design 8.2.5 Participant Diary 8.3 Adverse Events and Serious Adverse Events	Clarified solicited symptoms that are collected on the diary cards, including gas or flatulence; abdominal discomfort (distention, bloating, pain or cramping); diarrhea; vomiting; constipation, and oral temperature, should be recorded as adverse events only if they meet the CTCAE criteria.

Section # and Name	Description of Change
8.3.1 Time Period and Frequency for Collecting AE, AESI, SAE, and Other Reportable Safety Event Information	
6.6.4.1 Management of Invasive Infections 7.1.1 Study-wide Hold for Specified Safety Events	Specified which safety events would result in a study-wide hold and will be adjudicated by the study Data Monitoring Committee.
8.3.7 Adverse Events of Special Interest	Identified adverse events of special interest (AESIs) for the trial and clarified that serious AESIs will be adjudicated by the Data Monitoring Committee.
6.6.2 Dose Delays or Discontinuations Due to Toxicity 10.6 Contraceptive Guidance and Collection of Pregnancy Information	Updated Table 4, Table 6, and Appendix 6 to incorporate current nivolumab standards from the manufacturer.
Study Design	
Synopsis 3.0 Objectives and Endpoints 9.4.1.2 Secondary Endpoints 9.4.1.3 Exploratory Endpoints	Updated Objectives and Endpoint tables to clarify that progression of disease should be documented radiographically and to remove landmark analysis timepoints, allowing for greater flexibility of the final survival analysis.
Synopsis 1.2 Schema 1.3 Schedule of Activities 4.1.1 Cross-over for Participants in Group 2 or 3 4.4 Treatment Beyond Disease Progression 6.3.3 Unblinding 10.1.4 Informed Consent	Clarified requirements for participants in Groups 2 and 3 to cross-over to active SER-401 and nivolumab as part of Group 5.
Synopsis 1.2 Schema 1.3 Schedule of Activities 4.1 Overall Design 4.5 End of Study and End of Treatment Definitions 7.2 Participant Discontinuation/Withdrawal from Study	Clarified that individual participants will be active in the study for approximately 2 years. Defined End of Treatment date and End of Treatment visit.
1.2 Schema 1.3 Schedule of Activities	Clarified that the first follow-up visit will occur 100 days after the last dose of study intervention to align with standards.

Section # and Name	Description of Change
7.2 Participant Discontinuation/Withdrawal from Study 10.6.3 Pregnancy Testing	
6.5.3 Prohibited Therapy	Clarified that natural remedies may be permitted with Medical Monitor approval. Clarified the prohibition of live vaccines during the study.
Study Population	
Synopsis 4.1 Overall Design 5.2 Exclusion Criteria	Added criterion to allow participants with prior adjuvant anti-PD-1 therapy to enter into the study.
5.1 Inclusion Criteria	Clarified existing criterion that participants with only one measurable lesion by RECIST 1.1 must be discussed with the Medical Monitor prior to enrollment. Revised baseline AST and ALT values to < 3 x ULN at study entry.
5.2 Exclusion Criteria	Moved existing criterion from inclusion to the exclusion setting to enhance grammatical understanding. Continued to allow enrollment of participants who have received prior BRAF-targeted therapy and prior anti-CTLA-4. Clarified that there are no enrollment restrictions on participants with contrast allergies.
Study Intervention	
1.2 Schema 1.3 Schedule of Activities 4.1 Overall Design	Clarified that the oral FMT and matching placebo will be dispensed at the study site.
1.3 Schedule of Activities 4.1 Overall Design	Clarified that participants receiving SER-401 or matching placebo should observe at least a 6-hour fast prior to study intervention administration.
2.2.2 Combination of Oral Microbiome and Checkpoint Inhibitor Therapy 2.2.3 Background on Microbiome Study Intervention 2.3 Benefit/Risk Assessment 4.2 Scientific Rationale	Updated that the oral FMT used in the study will be from healthy donors whose stool has a “favorable” microbiome composition, instead of from donors with a response to checkpoint inhibitors.
2.3 Benefit/Risk Assessment	Updated benefit/risk of nivolumab to include additional approved indications set forth by the manufacturer.
4.1 Overall Design	Clarified grammar for the administration of SER-401/matching placebo and FMT/matching placebo.
6.6.1 Dose Reductions of Study Interventions	Improved grammar and clarified that no dose escalations or reductions to any study intervention are permitted. Improved grammar and clarified that no dose modifications for SER-401 or FMT are allowed.

Section # and Name	Description of Change
6.6.2 Dose Delays or Discontinuations Due to Toxicity	Improved grammar and clarified the circumstances for which dose delays and interruptions are allowed.
Study Assessments and Procedures	
1.3 Schedule of Activities 4.1 Overall Design 5.1 Inclusion Criteria 8.7 Biomarkers 8.7.3 Exploratory Biomarkers	Added language describing that the on-treatment biopsy should occur ideally from the same tumor lesion as the screening biopsy.
4.4 Treatment Beyond Disease Progression	Improved grammar and clarified the process for treating participants beyond disease progression and provided guidance for when treatment should be discontinued upon evidence of further progression.
8.2.5 Participant Diary	Clarified that the paper diary will be used as a tool to track solicited symptoms, not adverse events.
10.1.4 Informed Consent	Clarified circumstances when the participant will be asked to complete a new informed consent form.
Clarification of Document	
General Revisions	Document updated to address minor typographical errors and editorial changes for clarity. Provided updated references for USPIs, nivolumab immune-mediated adverse reactions management guide, and the CTCAE. Removed reference to IVRS throughout the document. Replaced acronym “SAERF” with “SAE report form” throughout the document.
Synopsis	Added table numbers to make navigation easier for the reader.
8.3.8.1 Emergency Medical Contacts	Updated the study Medical Monitor and contact information
10.6 Contraceptive Guidance and Collection of Pregnancy Information	Updated contraception guidance to align with current manufacturer standards

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol Title: A Multicenter Phase 1b Randomized, Placebo-controlled, Blinded Study to Evaluate the Safety, Tolerability and Efficacy of Microbiome Study Intervention Administration in Combination with Anti-PD-1 Therapy in Adult Patients with Unresectable or Metastatic Melanoma

Short Title: **M**elanoma **C**heckpoint and **G**ut Mic**r**obiome **A**lteration **w**ith Microbiome Intervention (MCGRAW)

Rationale:

This study is designed to evaluate the safety and tolerability of treatment with oral microbiome study interventions (fecal microbiota transplant [FMT] or SER-401) or matching placebo in combination with anti-programmed cell death 1 (anti-PD-1) therapy (nivolumab) in participants with unresectable or metastatic melanoma. The study also intends to assess clinical outcomes, the impact of microbiome study intervention administration on the microbiome profile, and its association with clinical and immunological outcomes.

Synopsis Table 1: Key Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To determine the safety of microbiome study intervention administration with anti-PD-1 therapy.	• Incidence and severity of AEs • Change from baseline in vital signs, clinical laboratory tests, electrocardiograms, and ECOG performance status.
Secondary	
• To evaluate the engraftment of FMT and SER-401 bacteria into the intestinal microbiome community in stool samples. • To assess the association of microbiome study intervention administration with clinical outcomes (objective response rate [ORR], disease control rate [DCR], progression-free survival [PFS] rate, overall survival [OS], and duration of response). • To assess the change in percentage of tumoral CD8 cells in tumor samples in response to anti-PD-1 therapy with or without microbiome study intervention administration.	• Determination of the engraftment of FMT or SER-401 bacteria into each of the microbiome study intervention groups relative to placebo. • ORR: Defined as CR or PR as best response by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 assessment. Participants who do not have RECIST assessment for any reason will be counted as not responding. • DCR: Defined as CR, PR, or stable disease (SD) for ≥ 24 weeks as best response by RECIST v1.1. Participants who do not have RECIST assessment for any reason will be counted as not responding. • PFS: Defined as the time from randomization to date of first documented radiographic progression of

Objectives	Endpoints
	disease or date of death due to any cause, whichever occurs first. • PFS rate at 1 year: Defined as the proportion of participants without documented progression of disease or death due to any cause at 1 year. • OS: Defined as the time from randomization until death due to any cause. • OS rate at 1 year: Defined as the proportion of participants alive at 1 year. • Duration of response: Defined as time from date of documented CR or PR to date of first documented radiographic progression of disease or date of death due to any cause, whichever occurs first. • Change in the percentage of CD8 cells in tumor tissue from baseline at Cycle 2.

AE = adverse event; CR = complete response; CTCAE = Common Terminology for Adverse Events; DCR = disease control rate; ECOG = Eastern Cooperative Oncology Group; ORR = objective response rate; OS = overall survival; PD-1 = programmed cell death-1; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; TOX = trial-limiting toxicities

Overall Design:

This is a Phase 1b, multicenter, randomized, placebo-controlled, blinded study in adult participants with unresectable or metastatic melanoma to evaluate the safety and tolerability of FMT, SER-401, or matching placebo in combination with anti-PD-1 therapy (nivolumab). Prior to initiating microbiome study intervention and nivolumab, participants will undergo an antibiotic or antibiotic placebo treatment lead-in to prime the gut microbiome for engraftment of the oral microbiome study intervention. Study intervention groups will be assessed for safety, changes in the microbiome, changes in percentage of tumoral CD8 T cells, and antitumor activity. Participants must have measurable disease that can be biopsied and consent to baseline and on-treatment biopsies, as well as stool and blood biomarker collection throughout the study.

Participants will be assigned to 1 of the 2 oral microbiome study interventions and randomized within each microbiome study intervention to the following groups:

- FMT: Group 1 (FMT) or Group 2 (FMT matching placebo)
- SER-401: Group 3 (SER-401 matching placebo) or Group 4 (SER-401)

Participants randomly assigned to receive placebo in Groups 2 or 3 and who have progression of disease while on study will be offered the option of receiving active SER-401 and nivolumab treatment as part of a cross-over to Group 5.

Number of Participants:

Approximately 60 participants will be treated. Since the primary objective is safety, no formal power/sample size computation is performed.

Enrollment caps will be utilized to ensure adequate representation of participants with low (ie, "unfavorable") fecal microbiome composition of the *Ruminococcaceae* abundance-based metric at screening. Each study intervention (FMT or SER-401) will enroll a minimum of 18 participants (60%) with low *Ruminococcaceae* (see Section 2.2.2).

Intervention Groups and Duration:

Participants will be assigned to 1 of the 2 oral microbiome study interventions (FMT or SER-401) by the Investigator based on clinical judgment and availability or feasibility of the interventions. Within each microbiome study intervention, participants will be randomized in a 2:1 ratio to the oral microbiome study intervention or matching placebo.

Prior to initiating the microbiome study intervention, participants will undergo a 4-day lead-in pretreatment with either antibiotic (vancomycin) or antibiotic placebo to prime the gut microbiome for engraftment of the oral microbiome study intervention, which will be administered following a 2-3 day washout.

Synopsis Table 2: Antibiotic/Microbiome Study Intervention Lead-in Doses and Schedule

Group	Antibiotic/Microbiome Study Intervention Assignment	Number of Participants	Antibiotic/Washout/Microbiome Lead-in (Dosing Schedule)		
			Antibiotic or PBO (Start Day -14)	ABX Washout (Day -10)	Microbiome Study Intervention (Day -7)
1	Vancomycin/ FMT Capsules	20	125 mg QID x 4 days	2 (+ 1) days[a]	FMT 10 capsules ($\geq 10^9$ CFU) QOD x 3[b]
2[c]	Placebo for Antibiotic/ FMT Matching Placebo	10	ABX PBO QID x 4 days	2 (+ 1) days[a]	FMT PBO 10 capsules QOD x 3[b]
3[c]	Placebo for Antibiotic/SER-401 Matching Placebo	10	ABX PBO QID x 4 days	2 (+ 1) days[a]	SER-401 PBO 2 capsules QD x 7
4	Vancomycin/SER-401	20	125 mg QID x 4 days	2 (+ 1) days[a]	SER-401 2 capsules (5×10^6 SCFU) QD x 7

ABX = antibiotic; CFU = colony forming units; FMT = fecal microbiota transplant; PBO = placebo; QD = every day; QID = 4 times daily; QOD = every other day; SCFU = spore colony forming units

[a] The washout duration will be a minimum of 2 days (48 hours), with a window of 1 additional day (24 hours), if needed to accommodate scheduling. Microbiome study intervention should be initiated no more than 3 days (72 hours) after stopping the antibiotic or antibiotic placebo.

[b] FMT or matching placebo will be administered QOD for 3 doses. If needed to accommodate scheduling, no more than 1 of the 3 doses may be administered with a window of 1 additional day (ie, dosing interval of up to 3 days instead of 2 days).

[c] Participants randomly assigned to receive placebo in Groups 2 or 3 and who have radiographic evidence of progression of disease while on study will be offered the option of receiving active SER-401 and nivolumab treatment as part of a cross-over to Group 5. Participants who agree to this option will follow the antibiotic/microbiome study intervention lead-in dose and schedule as shown for Group 4.

The protocol active treatment with anti-PD-1 therapy (nivolumab, 480 mg) will be administered intravenously (IV) according to institutional guidelines Q4W for up 12 cycles, unless the participant experiences confirmed disease progression or unacceptable toxicity in the judgment of the treating physician. A cycle is defined as 4 calendar weeks. Participants will be followed for approximately of 2 years from the time of the initiation of study intervention.

Synopsis Table 3: Microbiome Study Intervention/Anti-PD-1 Doses and Schedules

Group	Intervention Assignment	Number of Participants	Microbiome Study Intervention/ Anti-PD-1 (Dosing Schedule)		Anti-PD-1 (Dosing Schedule)
			Microbiome Study Intervention[a]	Anti-PD-1	
1	FMT Capsules/ Nivolumab	20	FMT 10 capsules ($\geq 10^9$ CFU) QW x 8 weeks	Nivolumab 480 mg Q4W	Nivolumab 480 mg Q4W
2[b]	FMT Matching Placebo/ Nivolumab	10	FMT PBO 10 capsules QW x 8 weeks	Nivolumab 480 mg Q4W	Nivolumab 480 mg Q4W
3[b]	SER-401 Matching Placebo/ Nivolumab	10	SER-401 PBO 2 capsules QD x 8 weeks	Nivolumab 480 mg Q4W	Nivolumab 480 mg Q4W
4	SER-401/ Nivolumab	20	SER-401 2 capsules (5×10^6 SCFU) QD x 8 weeks	Nivolumab 480 mg Q4W	Nivolumab 480 mg Q4W

CFU = colony forming units; PBO = placebo; PD-1 = programmed cell death-1; QD = every day; QID = 4 times daily; QOD = every other day; QW = every week; Q4W = every 4 weeks; SCFU = spore colony forming units

[a] Total duration of microbiome study intervention is 9 weeks (1-week lead-in + 8 weeks with anti-PD-1).

[b] Participants randomly assigned to receive placebo in Groups 2 or 3 and who have radiographic evidence of progression of disease while on study will be offered the option of receiving active SER-401 and nivolumab treatment as part of a cross-over to Group 5. Participants who agree to this option will follow the microbiome study intervention/anti-PD-1 dose and schedule as shown for Group 4.

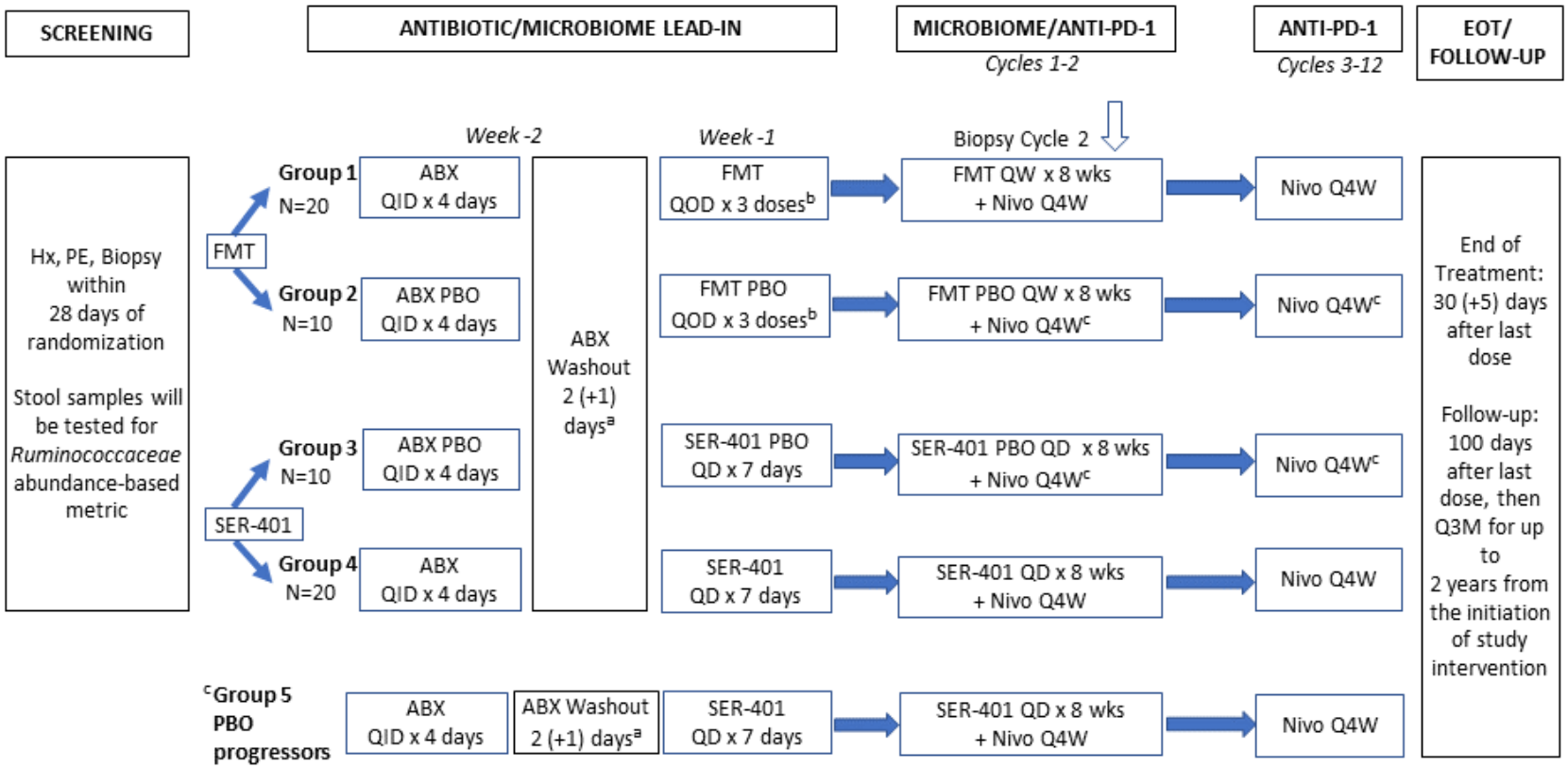
Administration of study intervention will be staggered by at least 1 day for the first 5 participants enrolled in each microbiome study intervention group (ie, FMT/matching placebo or SER-401/matching placebo) to monitor for safety.

Data Monitoring Committee: Yes (see Section 9.5.1)

1.2 SCHEMA

The study schema is depicted in Figure 1.

Figure 1: Study Schema



ABX = antibiotic (vancomycin); FMT = fecal microbiota transplant; Hx = history; N = number; PBO = placebo; PD-1 = programmed cell death-1 (nivolumab [Nivo]); PE = physical exam; QD = every day; QID = 4 times daily; Q3M = every 3 months; QOD = every other day; QW = every week; Q4W = every 4 weeks; wks = weeks

The protocol active treatment phase ends after up to 12 cycles of anti-PD-1 treatment (nivolumab), unless the participant experiences confirmed disease progression or unacceptable toxicity in the judgment of the treating physician. A cycle is defined as 4 calendar weeks. Participants will be followed for approximately 2 years from the time of the initiation of study intervention.

FMT requires frozen storage (≤ -65°C). FMT doses will be dispensed for administration at the study site. Participants in Groups 1 and 2 will come to the investigative site QOD for 3 doses during Week -1 and weekly for first 8 weeks of administration with nivolumab (Cycles 1 and 2).

SER-401 requires refrigerated storage (2° to 8°C). The first dose of SER-401 will be dispensed for administration in the clinic; subsequent doses will be self-administered by the participant at home. Participants in Groups 3, 4, and 5 will receive enough capsules to cover administration until the next clinic visit.

[a] The washout duration will be a minimum of 2 days (48 hours), with a window of 1 additional day (24 hours), if needed to accommodate scheduling. Microbiome study intervention should be initiated no more than 3 days (72 hours) after stopping the antibiotic or antibiotic placebo.

[b] FMT or matching placebo will be administered QOD for 3 doses. If needed to accommodate scheduling, either the second or third dose (but not both), may be administered with a window of 1 additional day (ie, dosing interval of up to 3 days instead of 2 days).

[c] Participants randomly assigned to receive placebo in Groups 2 or 3 and who have radiographic evidence of progression of disease while on study will be offered the option of receiving active SER-401 and nivolumab treatment as part of a cross-over to Group 5.

1.3 SCHEDULE OF ACTIVITIES

Table 1: Schedule of Activities

Tests & Procedures	Pre-Study Evaluations for Screening/ Enrollment[a]	On-Treatment Evaluation						End of Treatment[b]	Follow-up[c]	
		ABX/Microbiome Lead-in		Microbiome/ Anti-PD-1 Treatment		Anti-PD-1 Treatment				
		ABX Rx and Washout	Microbiome Study Intervention	Cycle 1	Cycle 2	Cycle 3	Cycles 4 – 12	30 days after last dose	First visit (100 days after last dose)[c]	Q3M for up to 2 years from initiation of study intervention[d]
Day	-43 to -15	-14	-7	Day 1	Day 1	Day 1	Day 1			
Window (days)		Refer to footnote m		± 1	± 3	± 3	± 3	+ 5		± 14
Informed consent[e]	X									
Review of I/E criteria	X									
Medical, cancer history	X									
Physical examination	X			X	X	X	X	X	X	
Pregnancy test (serum or urine)	X	X		X	X	X	X	X	X	
ECOG performance status	X		X	X	X	X	X	X	X	
Vital signs (see Section 8.2.3)	X	X	X	X	X	X	X	X	X	
Body weight	X	X	X	X	X	X	X	X		
Hematology (see Table 7)	X		X	X	X	X	X	X	X	
Clinical chemistry (see Table 7)	X		X	X	X	X	X	X	X	
Urinalysis	X		X	X	X	X	X	X	X	
12-lead ECG	X			X		X				
cfDNA (blood)[f]	X				X		X[f]	X		
Circulating soluble analytes[g]	X		X	X	X	X	X[g]	X		
Blood immune biomarkers[g]	X		X	X	X	X	X[g]	X		

Tests & Procedures	Pre-Study Evaluations for Screening/ Enrollment[a]	On-Treatment Evaluation						End of Treatment[b]	Follow-up[c]	
		ABX/Microbiome Lead-in		Microbiome/ Anti-PD-1 Treatment		Anti-PD-1 Treatment				
		ABX Rx and Washout	Microbiome Study Intervention	Cycle 1	Cycle 2	Cycle 3	Cycles 4 – 12	30 days after last dose	First visit (100 days after last dose)[c]	Q3M for up to 2 years from initiation of study intervention[d]
Day	-43 to -15	-14	-7	Day 1	Day 1	Day 1	Day 1			
Window (days)		Refer to footnote m		± 1	± 3	± 3	± 3	+ 5		± 14
Stool collection	X[h]	X[i] (to be collected following completion of ABX or ABX placebo and prior to starting microbiome study intervention)		X[h] (Day 1 and Day 8)	X	X	X[h] (Cycle 4 and Cycle 7)	X[h]		
Tumor biopsy[i]	X				X (Cycle 2, Days 2-12)			X[i] (at PD)		
Concomitant medications	X	X	X	X	X	X	X	X	X	
Adverse events	All AEs, AESIs, and SAEs will be collected for at least 100 days after the last dose of study intervention.[b,j] The first 5 participants enrolled in each microbiome study intervention group (ie, FMT/matching placebo or SER-401/matching placebo) will be contacted twice during Cycle 1 (once between Days 2-4 and once on Day 7 [± 1 day to accommodate weekends or holidays]) to assess for emerging AEs that may require early intervention.									
Randomization		X[k]								
Participant-reported diary for: • solicited symptoms • recording body temperature • tracking study intervention compliance		Participants will: • record safety events commonly associated with microbiome study intervention on a daily basis from Day -7 through the end of Cycle 1 • measure and record body temperature on a daily basis from Day -7 through Day 1 • track compliance to the self-administered oral antibiotic and SER-401 from Day -14 through the end of Cycle 2								
Collection of participant-reported diary[l]		X	X	X	X	X				

Tests & Procedures	Pre-Study Evaluations for Screening/ Enrollment[a]	On-Treatment Evaluation						End of Treatment[b]	Follow-up[c]	
		ABX/Microbiome Lead-in		Microbiome/ Anti-PD-1 Treatment		Anti-PD-1 Treatment				
		ABX Rx and Washout	Microbiome Study Intervention	Cycle 1	Cycle 2	Cycle 3	Cycles 4 – 12	30 days after last dose	First visit (100 days after last dose)[c]	Q3M for up to 2 years from initiation of study intervention[d]
Day	-43 to -15	-14	-7	Day 1	Day 1	Day 1	Day 1			
Window (days)		Refer to footnote m		± 1	± 3	± 3	± 3	+ 5		± 14
Oral vancomycin/placebo pretreatment[m]		X								
Oral microbiome administration (based on randomization)										
Groups 1 and 2: FMT capsules or matching placebo[n]			QOD x 3 doses[n]	QW x 8 weeks (ie, Cycles 1 and 2)						
Groups 3 and 4 (and 5): SER-401 or SER-401 matching placebo[o]			QD x 7 doses	QD x 8 weeks (ie, Cycles 1 and 2)						
Nivolumab administration[p]				X	X	X	X			
Disease assessment[q]	X (Day -29 to Day -15)			Repeat every 12 weeks (± 1 week) from Cycle 1, Day 1 until radiographic PD or the start of subsequent therapy						
Follow-up for overall survival									X	X

ABX = antibiotic; AE(s) = adverse event(s); AESI(s) = adverse event(s) of special interest; cfDNA = cell-free deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ED = early discontinuation; EOT = end of treatment; FMT = fecal microbiota transplant; I/E = inclusion/exclusion; LDH = lactate dehydrogenase; PD = progressive disease; PD-1 = programmed cell death-1; QD = every day; QID = 4 times daily; Q3M = every 3 months; QOD = every other day; QW = every week; Q4W = every 4 weeks; SAE(s) = serious adverse event(s)

[a] Tests/procedures performed as standard of care prior to obtaining informed consent and within 28 days prior to randomization do not have to be repeated at screening.

[b] The End of Treatment Visit will be completed following the last dose of study intervention (ie, after 12 cycles of study intervention or at early discontinuation). All participants, including those who discontinue early after receiving any study intervention, should have the End of Treatment visit to complete the visit procedures. The visit at which disease assessment shows progressive disease may be used as the End of Treatment visit if it occurs 30 (+5) days after the last dose of nivolumab. Every effort should be made to complete the visit within the 30 (+5) day window; however, the visit should be conducted even if outside the window. Participants who have received any microbiome study intervention should continue to be followed for SAEs and AESIs up to 26 weeks after the last dose of microbiome study intervention (see Section 8.3.1).

[c] At least one hundred (100) days after the last dose there is a visit with assessments ***if no alternative therapy has started*** (continued administration of monotherapy nivolumab beyond the 12 cycles administered in this clinical trial will not be considered alternative therapy). If the participant has started alternative therapy within that 100 days after the last dose, the first follow up visit will be contact by telephone only. AEs, concomitant medications, or other assessments are reported up to the date of start of alternative therapy.

[d] For approximately 2 years from the initiation of study intervention, participants will be contacted by telephone every 3 months to determine their survival status.

[e] Participants randomly assigned to receive placebo in Groups 2 or 3 and who have radiographic evidence of progression of disease while on study will be offered the option of receiving active SER-401 and nivolumab treatment as part of a cross-over to Group 5. Participants who agree to this option will provide informed consent and will enter Group 5.

[f] cfDNA (blood) will be assessed at screening, Cycle 2 Day 1, Cycle 4 Day 1, and EOT.

[g] Circulating soluble analytes and blood immune biomarkers will be assessed at screening, Microbiome Lead-in (Day -7), Cycle 1 Day 1, Cycles 2-4 Day 1, and EOT.

[h] Stool will be collected at screening for assessment of the fecal microbiome composition of the *Ruminococcaceae* abundance-based metric for stratification and other microbiome assessments. A second screening collection will be allowed if the results of the initial screening collection are indeterminate. Following randomization, stool will be collected with a window of up to 2 days prior to the following timepoints, when feasible: start of microbiome study intervention (ie, collected after completion of ABX or ABX placebo and prior to the start microbiome study intervention) and Cycle 1 Day 1 (ie, 7 days after start of microbiome study intervention). Thereafter, stool will be collected with a window of ± 3 days of the following timepoints, when feasible: Cycle 1 Day 8 (ie, 7 days after first dose of nivolumab); Cycle 2 Day 1; Cycle 3 Day 1; Cycle 4 Day 1 (ie, 4 weeks after last dose of microbiome study intervention); Cycle 7 Day 1; and at EOT.

[i] Participants will undergo 2-3 tumor biopsies: prior to beginning any protocol therapy including antibiotic treatment (ie, baseline biopsy, mandatory), and during treatment (ie, on-treatment biopsy during Cycle 2, if medically feasible). On-treatment biopsy should occur as early as possible after the second dose of nivolumab (ie, Cycle 2, Day 2 – Day 12); however, any on-treatment biopsy after Day 1 of Cycle 2 will be accepted. An optional biopsy may be obtained during the course of the study or at the time of disease progression, including from participants who respond and subsequently progress.

[j] All SAEs will be collected from the time the participant signs informed consent. All AEs, including AESIs, will be collected from the start of study intervention.

[k] Randomization occurs prior to ABX administration.

[l] Participants will be asked to bring the participant diary to each clinical visit so that the clinical staff can record the compliance and safety information on an ongoing basis.

[m] Four days of oral QID vancomycin (125 mg) or placebo pretreatment, which can be self-administered at home, followed by a washout prior to starting microbiome study intervention. The washout duration will be a minimum of 2 days (48 hours), with a window of 1 additional day (24 hours), if needed to accommodate scheduling. Microbiome study intervention should be initiated no more than 3 days (72 hours) after stopping the antibiotic or antibiotic placebo.

[n] The first dose of FMT or matching placebo will be administered in the clinic and will be followed by a 1-hour observation period after dosing. The participant should have nothing by mouth for 4 hours prior to and 45 minutes following FMT administration. Subsequent doses of FMT or matching placebo will be dispensed for administration at the study site. FMT or matching placebo will be administered QOD for 3 doses for the first week. If needed to accommodate scheduling, no more than 1 of the 3 doses may be administered with a window of 1 additional day (ie, dosing interval of up to 3 days instead of 2 days). Tests and procedures as indicated are required at the time of the first dose (Day -7) only and do not need to be repeated at the visits for the second and third doses. Starting on Cycle 1 Day 1, FMT or matching placebo will be administered QW for 8 weeks.

[o] The first dose of SER-401 or matching placebo will be administered in the clinic and will be followed by a 1-hour observation period after dosing. SER-401 should be taken at approximately the same time on each day. The participant should observe an overnight or at least a 6-hour fast (no food or drink except for small amounts of water) prior to SER-401 administration. Subsequent doses of SER-401 or matching placebo will be dispensed to the participant for self-administration QD at home. Compliance will be recorded on the participant-reported diary.

[p] Nivolumab will be administered at a dose of 480 mg IV over 30 minutes Q4W starting on Day 1 of Cycle 1 and will continue for up to 12 cycles, unless the participant experiences confirmed disease progression or unacceptable toxicity in the judgment of the treating physician. A cycle is defined as 4 calendar weeks. The time between nivolumab doses should not be less than 25 days.

[q] Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to randomization do not have to be repeated at screening. Tumor assessments should be performed every 12 weeks until radiographic PD or the start of subsequent therapy.

2 INTRODUCTION

2.1 STUDY RATIONALE

This study is designed to evaluate the safety and tolerability of treatment with oral microbiome study interventions (fecal microbiota transplant [FMT] or SER-401) or matching placebo in combination with anti-programmed cell death 1 (anti-PD-1) therapy (nivolumab) in participants with unresectable or metastatic melanoma. The study also intends to assess clinical outcomes, the impact of microbiome study intervention administration on the microbiome profile, and its association with clinical and immunological outcomes.

2.2 BACKGROUND

Melanoma is a deadly form of skin cancer with an incidence that is rising rapidly (Tripp et al., 2016). It was estimated that 80,000 patients would be diagnosed with melanoma in 2017 in the United States, with over 10,000 patients dying of metastatic disease (Siegel et al., 2017). Melanoma disproportionately causes a significant number of life years lost per cancer-related death, resulting in substantial financial burden (US $3.5 billion per year) (Ekwueme et al., 2011). Historically, < 10% of patients with stage IV melanoma achieve long-term (> 5 years) survival (Balch et al., 2010).

Four immune checkpoint inhibitor (CPI) monotherapy or combination regimens, each of which can produce long-term clinical benefit, have been approved since 2011 for the treatment of patients with stage IV melanoma. Ipilimumab, a humanized antibody that blocks cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) on the surface of T cells, approved in 2011, achieves clinical responses in ~10% of patients, but results in 3 year overall survival (OS) rates of ~22% with many durable responses (Hodi et al., 2010; Balch et al., 2010; Schadendorf et al., 2015). Nivolumab and pembrolizumab, approved in 2014, are antibodies against PD-1 on the surface of T cells; both achieve clinical responses in 35-45% of treatment-naïve patients, with most responses lasting >2 years (Hodi et al., 2010; Ribas et al., 2016). Importantly, high-grade toxicity rates are much lower for the more active anti-PD-1 therapies (8%) compared with ipilimumab (27%) (Robert et al., 2015a). While the results with single-agent anti-PD-1 therapy are impressive, combined treatment with ipilimumab and nivolumab (FDA-approved 2015) produces clinical responses in 55-60% of metastatic melanoma patients (Ribas et al., 2017; Larkin et al., 2015). The increased activity of ipilimumab/nivolumab, however, is accompanied by increased side effects; 55% of patients experience significant toxicities, some long lasting or lethal, and ~30% of patients have to stop treatment due to toxicity. Thus, there is a critical need to develop new approaches that are safer, and which may also overcome resistance in patients who fail this treatment.

2.2.1 Microbiome Modulation

The microbiome is the collection of microbes – bacteria, viruses and fungi – that live on and in the human body. The composition of the gut microbiome has received particular scientific attention due to its correlation with various disease processes. Our understanding of the bacterial component of the gut microbiome in particular has been advanced in the last decade due to the use of next generation sequencing to elucidate the complex and variable ecology of commensal species and pathobionts (commensal species that, under certain circumstances can play a role in disease). The gut microbiome is thought to play a role in health in the following broad ways: promoting resistance to colonization and infection by pathogenic bacteria; educating and regulating the immune system; maintaining gut epithelial barrier integrity; modulating host metabolism; and potentially altering the function of the central nervous system (Lynch and Pedersen, 2016).

Fecal microbiota transplant (FMT) is a procedure where minimally processed stool is transferred from a donor to a person with disease. FMT can be administered via oral capsules (Youngster et al., 2016), nasogastric or nasoduodenal tube, colonoscopy or enema. FMT has been shown to prevent recurrence of *Clostridium difficile* infection (CDI), and reported rates of efficacy vary from 50% to 90+%. However, the largest blinded, randomized, placebo-controlled study using enema delivery suggested prevention of recurrence in 63.9% of subjects receiving FMT compared to 45.5% for placebo ($p = 0.046$, Dubberke et al., 2016). The other indication in which FMT has shown efficacy in blinded, randomized, placebo-controlled setting is active, mild-to-moderate ulcerative colitis with remission rates of ~20% above placebo (Moayyedi et al., 2015; Paramsothy et al., 2017). Unlike CDI, efficacy in treating active ulcerative colitis requires repetitive FMT, for instance weekly or daily over a 6-8 week period. FMT is generally regarded as well tolerated with adverse events (AEs) limited to nausea, vomiting, fever, abdominal pain, and diarrhea (Vermeire et al., 2016; Pigneur and Sokol, 2016). While FMT has been evaluated in other disease conditions, there is as yet no compelling evidence for clinical utility for indications other than CDI.

The activity of repetitive FMT in the setting of ulcerative colitis demonstrates the causal relationship between microbiome composition and immune tone. In animal models and studies in human cohorts, bacterial genera such as *Bacteroides*, *Clostridium*, and *Faecalibacterium* have been reported to modulate antitumor immunity via expansion of T-regulatory cells, activation of dendritic cells or secretion of anti-inflammatory cytokines (Gopalakrishnan et al., 2018, Sivan et al., 2015; Routy et al., 2018; Matson et al., 2018). The link between gut microbiota composition and immune state has prompted an evaluation in cancer and particularly, in regard to treatment with immunotherapy such as CPI (NCT03353402; NCT03341143; NCT03637803).

SER-401 is a spore preparation made from the stool of a healthy donor whose fecal microbiome embodies characteristics of the "favorable" microbiome profile identified by Gopalakrishnan et al. (Gopalakrishnan et al., 2018) as discussed in Section 2.2.3. Spore preparations from healthy donors that embody characteristics of the "favorable" microbiome have been shown to be efficacious in improving response to anti-PD-1 treatment in several mouse models of cancer (SER-TSC-18-002 Report, 2018; SER-TSC-18-003 Report, 2018; SER-TSC-18-006 Report, 2018).

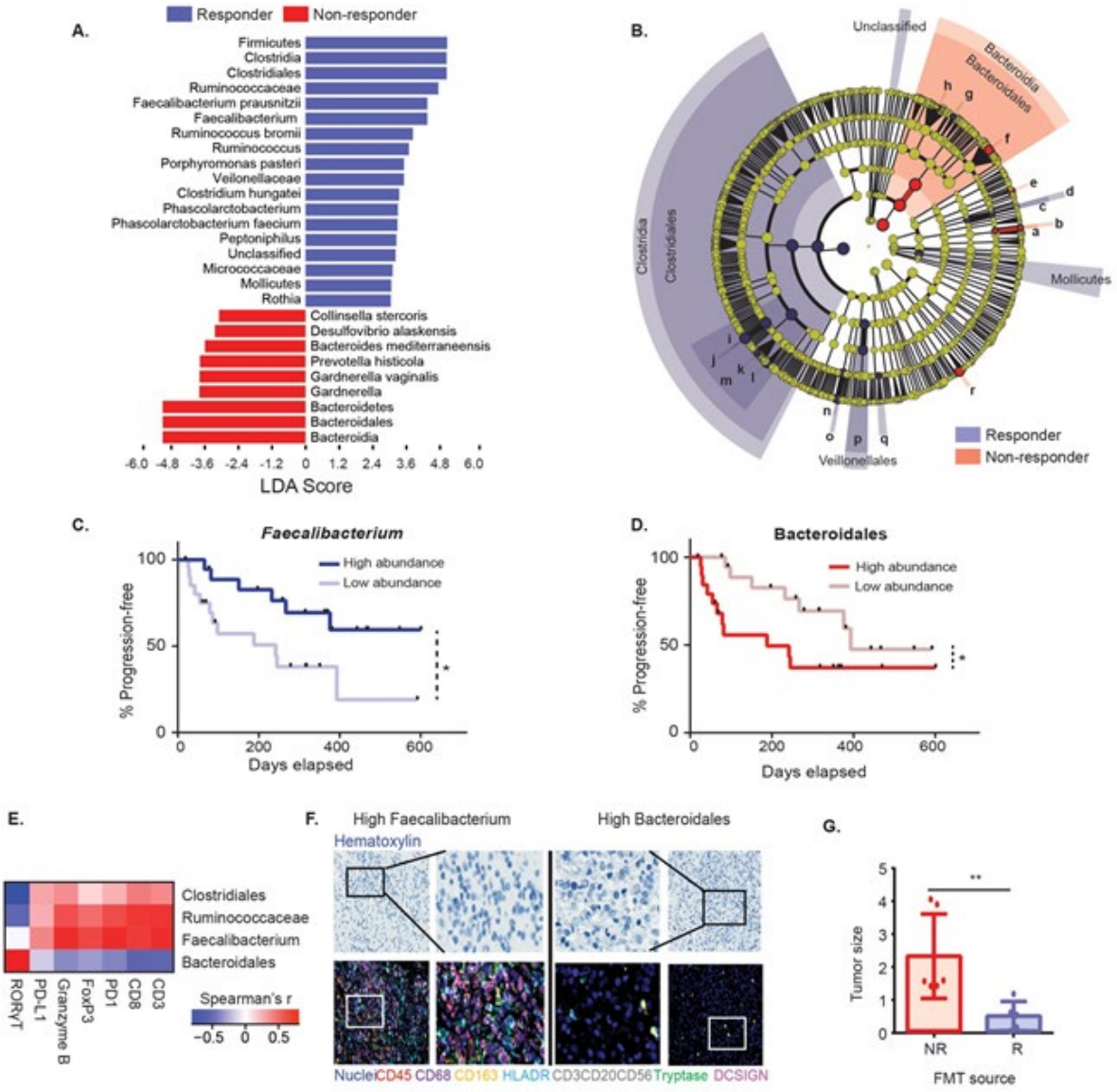
2.2.2 Combination of Oral Microbiome and Checkpoint Inhibitor Therapy

Despite the impressive benefits of single-agent CPI in patients with Stage IV melanoma, less than 10% of patients achieve complete response to therapy (Robert et al., 2015a; Robert et al., 2015b; Ribas et al., 2016). While CPI is now standard-of-care for the treatment of advanced metastatic melanoma patients, there is a global effort to improve response to these therapies in order to extend this benefit to the majority of patients, most of whom will die as a result of their cancer.

The microbiome of metastatic melanoma patients prior to treatment with anti-PD-1 monoclonal antibody has been studied by investigators at the University of Texas MD Anderson Cancer Center (MDACC). These findings, which were recently published (Gopalakrishnan et al., 2018), demonstrate that the pretreatment composition of the fecal microbiome in patients who respond to anti-PD-1 therapy (responder [R]) has a distinct bacterial signature compared to patients who do not respond to anti-PD-1 therapy (non-responder [NR]). Specifically, higher alpha-diversity (ie, a higher number of different species) and relative abundance of the bacterial genus *Faecalibacterium* (within the order Clostridiales and Family *Ruminococcaceae*) was associated with better treatment response and prolonged progression-free survival (PFS) (Figure 2A-C). Conversely, lower alpha-diversity and higher abundance of the bacterial order Bacteriodales was associated with lack of treatment response and shorter PFS (Figure 2A-B, D). The bacterial signature in patients who achieved a response to anti-PD-1 treatment was also associated with a more favorable tumor immune profile in a subset of melanoma patients with available tumor samples (Figure 2E-F). Analysis of the stool microbiome and clinical response to anti-PD-1 treatment from an additional cohort of metastatic melanoma patients also supported the use of a *Ruminococcaceae* abundance-based metric (unpublished data). Across the Gopalakrishnan study (43 patients), the additional cohort (69 patients), and the combined dataset (112 melanoma patients), *Ruminococcaceae* family abundance, and the higher order taxa containing *Ruminococcaceae*, were the only common statistically significant enrichment in Responders vs Non-responders.

In order to evaluate causality in a preclinical model, the MDACC team transplanted the fecal microbiota (FMT) from human melanoma patients who either responded to CPI (Rs) or failed to respond to CPI (NRs) into germ free mice via oral gavage. After several weeks for microbiome equilibration, syngeneic murine tumors were implanted, and mice were treated with CPI (anti-programmed cell death ligand 1 [PD-L1] antibody). Mice who received FMT from R patients experienced a significantly lower tumor burden and improved responses to PD-L1-based therapy compared to mice who received NR FMT (n = 6, Figure 2G). The differences in tumor size (expressed as a fold change relative to control) were computed using the Mann-Whitney test ($p < 0.01$). Fecal microbiota transplant alone was not evaluated in these preclinical studies as it has been reported to have minimal antitumor activity as a single agent treatment (Matson et al., 2018).

Figure 2: Differential Gut Microbiota in Responders (R) and Non-responders (NR) to Anti-PD-1 Therapy are Associated with Differential Immune Infiltrates



A) Linear discriminant analysis (LDA) scores computed for differentially-abundant taxa in the fecal microbiomes of R (blue) and NR (red). Length indicates effect size associated with a taxon. p=0.05 for the Kruskal-Wallis test; LDA score > 3. B) Taxonomic cladogram from LEfSe showing differences in fecal taxa. Dot size is proportional to the abundance of the taxon. Letters correspond to the following taxa: (a) Gardnerella vaginalis (b) Gardnerella (c) Rothia (d) Micrococcaceae (e) Collinsella stercoris (f) Bacteroides mediterraneensis (g) Porphyromonas pasteri (h) Prevotella histicola (i) Faecalibacterium prausnitzii (j) Faecalibacterium (k) Clostridium hungatei (l) Ruminococcus bromii (m) Ruminococcaceae (n) Phascolarctobacterium faecium (o) Phascolarctobacterium (p) Veilonellaceae (q) Peptoniphilus (r) Desulfovbrio alaskensis. Comparison Kaplan Meier (KM) PFS curves by long-rank test in patients with C) high (dark blue, n=19, median PFS=undefined) or low (light blue, n=20, median PFS=242 days) abundance of Faecalibacterium (top) or D) high (dark red, n=20, median PFS=188 days) or low (light red, n=19, median PFS=393 days) abundance of Bacteroidales (bottom). E) Pairwise Spearman rank correlation heatmap of significantly different taxa in fecal samples (n=15) at baseline and CD3, CD8, PD-1, FoxP3, GzmB and RORγT density and PD-L1 by H-score in matched tumors. (F) Representative multiplex IHC

images and (G) Difference in size by MW test of tumors at day 14, implanted in R-FMT (blue) and NR-FMT mice (red) expressed as fold change (FC) relative to average tumor volume of Control GF mice. Data from 2 independent FMT experiments (R-FMT, n=5, median FC=0.18; NR-FMT, n=6, median FC=1.52).

Based on these analyses, healthy donors whose stool has a "favorable" microbiome composition of high *Ruminococcaceae*, similar to that of melanoma patients who achieved a response to anti-PD-1 treatment, will be enrolled in a stool donor collection protocol for the oral FMT manufacturing to be used in this study. *Ruminococcaceae* abundance for an "unfavorable" microbiome will be used as a stratification metric for this study.

2.2.3 Background on Microbiome Study Intervention

Support for the use of microbiome study intervention is provided in Section 2.2.1.

Two investigational microbiome products will be used in this program. The FMT investigational product will be collected and processed from qualified healthy donors according to established FMT procedures described by Massachusetts General Hospital (MGH) Investigational New Drug (IND) 16011. The FMT will be delivered in capsule form. This group is intended to test the safety of an intervention whose composition is enriched in the family *Ruminococcaceae* that is characterized as a "favorable" microbiome (Gopalakrishnan et al., 2018). By virtue of possessing spore formers and non-spore formers, the FMT investigational product represents a broader set of bacterial taxa. It will be administered at a dose and regimen consistent with a prior study of FMT in chronic disease settings (NCT02530385).

SER-401 is an investigational product containing microbial spores purified from the stool of qualified healthy donors and delivered in capsule form. This group is intended to test the safety of an intervention whose composition is enriched in spore-forming members of the family *Ruminococcaceae* that is characterized as a "favorable" microbiome (Gopalakrishnan et al., 2018). It will be administered at a dose and regimen similar to that used in prior studies of spore-based products for the treatment of active mild-to-moderate ulcerative colitis (NCT02618187).

The study design, evaluating FMT and SER-401 in the same clinical study, provides the opportunity to define how the participant's microbiome influences CPI therapy outcomes by including a wide range of bacterial species from 2 microbiologically-diverse investigational drug products. The aim of this clinical study is to determine:

(1) safety and tolerability of each study intervention group (microbiome study interventions or matched placebo, each combined with anti-PD-1 therapy).

(2) whether microbiome administration increases the percentage of tumoral CD8 cells and enhances response to anti-PD-1 therapy as determined by clinical endpoints of ORR, DCR, PFS, and OS; and if so,

(3) the changes in the fecal microbiome as a result of administration of microbiome study intervention, and, in an exploratory setting, to identify species and metabolites that correlate with clinical and immunological outcomes.

2.2.4 Background on Nivolumab

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response. Opdivo® (nivolumab) is approved in the US for the treatment of several cancer types, including unresectable or metastatic melanoma (as monotherapy or in combination with ipilimumab) and as monotherapy in previously-treated metastatic non-small cell lung cancer (NSCLC), advanced renal cell carcinoma (RCC), relapsed or refractory classical Hodgkin lymphoma (cHL), locally advanced or metastatic urothelial carcinoma; recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN), microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC), and hepatocellular carcinoma (HCC).

Refer to the approved prescribing information (Opdivo USPI, 2019) for detailed background information on nivolumab.

2.3 BENEFIT/RISK ASSESSMENT

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy in several tumor types, including NSCLC, melanoma, RCC, cHL, small cell lung cancer, SCCHN, urothelial cancer, HCC, and MSI-H or dMMR CRC. In confirmatory trials, nivolumab demonstrated a statistically significant improvement in OS as compared with the current standard of care in subjects with unresectable or metastatic melanoma, advanced or metastatic NSCLC, advanced RCC, or SCCHN.

The safety profile of nivolumab monotherapy is similar across tumor types. There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. In Phase 3 controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical efficacy, and manageable using established safety guidelines. Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and timely immunosuppressive therapy or other supportive care (Opdivo USPI, 2019).

Overall, these findings support a favorable benefit-risk profile for nivolumab across various tumor types. More detailed information about the known and expected benefits and risks and reasonably expected AEs of nivolumab may be found in the prescribing information (Opdivo USPI, 2019).

Fecal microbiota transplantation (FMT) has emerged as an important tool for investigating the role of the microbiome in humans. FMT is most commonly used for preventing *Clostridium difficile* recurrence in patients with multiple recurrent infections and is considered standard of care (McDonald et al., 2018). Due to its reported safety profile (see below), the experimental use of FMT has expanded to include indications as diverse as inflammatory bowel disease (IBD), hepatic encephalopathy, autism spectrum disorder, metabolic syndrome and Parkinson's disease (reviewed in Choi and Cho, 2016). Indeed, there are now studies in patients with refractory melanoma evaluating FMT derived from stool donor(s) who were responders to CPI treatment (NCT03353402) or FMT derived from stool donors who were complete responders to CPI in combination with anti-PD-1 treatment (NCT03341143). A third study is evaluating microbiome drug product in combination with anti-PD-1 treatment in patients with solid tumors (NCT03637803).

Short-term reported adverse events following FMT include abdominal discomfort, bloating, flatulence, diarrhea, vomiting, fever, and constipation (Choi and Cho, 2016). IBD flares have been reported in patients with a history of IBD in multiple studies, including those not being actively treated for IBD (Qazi et al., 2017). Procedural complications, including perforations and bleeding following endoscopy or pulmonary aspiration following naso-duodenal administration, have also been reported (Choi and Cho, 2016). The long-term evaluation of FMT safety has been limited since most CDI studies are IND-exempt and conducted by individual investigators or physicians. Potential serious adverse events (SAEs) include infection by undetected or unscreened enteric pathogens (bacteria, viruses, fungi and protists) present in the FMT product (Wang et al., 2016), and mortality (Lee et al., 2016; Dubberke et al., 2018). In addition to the risk of transfer of infectious agents, additional potential concerns include increased frequency of metabolic disorders such as diabetes, obesity or liver disease including non-alcoholic steatohepatitis, irritable bowel syndrome (IBS), immunological/inflammatory disorders such as IBD, asthma and autoimmune conditions. Most of these long-term concerns have not been reported but have a scientific basis due to the association of the microbiome in humans with many of these diseases. There is one case report suggesting the transmission of obesity from stool donor to the FMT patient in the setting of CDI (Alang and Kelley, 2015).

Several studies have shown that following FMT delivered via colonoscopy or enema, the recipient microbiome changes within days and tends to be more similar to the donor than the pre-FMT baseline (Hamilton et al., 2013; Weingarden et al., 2015; Khanna et al., 2017). There can be variation in the recipient's microbiome composition over time. The donor-recipient similarity is strongest immediately following FMT; as time progresses, the patient tends to diverge from the donor microbiome profile, and the patient's microbiome assumes a unique composition, distinct from either the donor or the starting state post-antibiotics (Hamilton et al., 2013; Weingarden et al., 2015; Khanna et al., 2017).

Frozen oral formulations of FMT have been reported in the literature for patients with recurrent CDI (Youngster et al., 2016). Participants with CDI received a regimen of 15 FMT capsules orally per day for 2 days. Resolution of diarrhea was observed in 14/20 (70%) patients after a single regimen with no serious adverse events attributed to the treatment. Of the 6 non-responders, 4 responded to a subsequent treatment (Youngster et al., 2016), demonstrating that oral administration of frozen FMT capsules can be effective in the treatment of CDI and restructures the gut microbiome.

SER-401 is a purified suspension of *Firmicute* spores derived from a donor whose microbiome meets the *Ruminococcaceae* metric characterized as favorable (Gopalakrishnan et al., 2018). While SER-401 has not been evaluated in humans, related donor-derived spore products, SER-109 and SER-287, have been evaluated in clinical studies in subjects with recurrent CDI and ulcerative colitis ([UC]; NCT02437487; NCT02618187) at a dose of 1 x 10^8 SporQs ("spore equivalents", a biochemical measure of spore content equivalent to approximately 1 x 10^7 spore colony-forming units [SCFUs]) in 1 or 2 doses (SER-109) or a weekly or daily dose for up to 8 weeks (SER-287).

Subjects with multiply recurrent CDI or with mild-to-moderate UC may differ from individuals considering a study of SER-401. In Seres' studies of SER-109, the average age of subjects who received SER-109 was ~ 65 years, whereas in studies with SER-287, the average age of subjects was 47 years. This difference may influence the AEs that may be anticipated in subjects administered SER-401.

In 3 completed clinical studies (SERES-001, SERES-004, and SERES-005) a total of 141 subjects received 1 or 2 doses of SER-109. The available safety data from these 3 studies, including 2 open-label studies and 1 placebo-controlled study, suggest that SER-109 is safe and well-tolerated in subjects with multiply recurrent CDI, although in these subjects SER-109 is associated with a slight increase in gastrointestinal (GI) AEs, particularly diarrhea, compared with placebo (25% vs. 14%, respectively).

Across completed studies of SER-109 as of April 19, 2017, 87% of the subjects (123/141) who had received 1 or 2 doses of SER-109 had experienced at least one AE. Most adverse events were mild to moderate in intensity, and the most common events (ie, incidence ≥ 5% in either study) were GI disorders. Overall, 24% (34/141) of subjects had an AE reported to be related to SER-109 (ie, probably or likely due to SER-109). In total, 15% of subjects who had received SER-109 (21/141) had experienced at least 1 SAE; however, no SAEs were reported to be related to SER-109. There have been 6 deaths in subjects who received SER-109, all of which were unrelated to SER-109 and 1 of which occurred after the subject left the study.

Clinical experience with SER-287 includes a completed Phase 1b study (SERES-101), a multicenter, randomized, double-blind, placebo-controlled, multiple dose study that evaluated

the safety and tolerability of SER-287, in addition to the microbiome alterations and pharmacodynamics associated with 2 dosing regimens of SER-287 in adult subjects with active mild-to-moderate UC. The study enrolled a total of 58 subjects who were randomized into 1 of 4 treatment groups; endpoints were assessed following a 6-day pretreatment period (vancomycin or placebo) followed by an 8-week induction treatment period (SER-287 or matching placebo). This regimen is similar to the proposed use of SER-401.

As of September 19, 2017, safety information was available for all subjects who were followed for up to 92 days (11.5 weeks), including subjects who withdrew from the study at an earlier time point. Forty-seven subjects received SER-287; 15 subjects received daily SER-287 and 32 subjects received weekly SER-287. The available safety data from this study suggest that SER-287 is safe and well-tolerated in subjects with UC, with a safety profile similar to placebo.

Among the 47 subjects who received SER-287:

- Overall, there were a total of 91 treatment-emergent adverse events (TEAEs) reported in subjects who received SER-287; all were considered to be mild to moderate in intensity. A total of 66% of subjects (31/47) who received SER-287 experienced at least 1 TEAE.
- 27.7% of subjects (13/47) had a least 1 TEAE reported to be related to SER-287, the most common being abdominal pain (8.5% compared with 0% in the placebo group) and diarrhea (6.4% compared with 9.1% in the placebo group).
- There was one SAE (worsening depression in a subject with a history of depression), which was considered not to be related to study drug by the investigator.
- There were no deaths in the study.

One of the primary objectives of the SER-287 Phase 1b UC trial was to determine the engraftment of SER-287 bacteria in each of the treatment groups relative to placebo. The data support oral administration of a spore-based microbiome drug product following vancomycin pretreatment and demonstrate conversion to the *Ruminococcaceae* metric characterized as a favorable in the majority of the UC participants (SER-DSC-0043 Report, 2018). In the absence of antibiotic pretreatment, engraftment of SER-287 was neither robust nor durable. SER-287 given daily after vancomycin led to rapid engraftment which reached a maximum by Day 10. Engraftment did not change between Day 56, the last day of treatment, and 4 weeks thereafter, consistent with properties expected of a living drug.

In addition, clinical remission and endoscopic improvement were improved with daily dosing compared with weekly dosing of SER-287.

Overall, these findings support a favorable benefit-risk profile for FMT and SER-401 in humans across a range of diseases. The treatment of participants with metastatic melanoma with oral FMT or SER-401 in combination with anti-PD-1 therapy is expected to be safe and tolerable. Additionally, we postulate that treatment with oral FMT or SER-401 will favorably impact the microbiome profile of participants treated with the combination and correlate with clinical outcomes.

3 OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are listed in Table 2.

Table 2: Objectives and Corresponding Endpoints

Objectives	Endpoints
Primary	
• To determine the safety of microbiome study intervention administration with anti-PD-1 therapy.	• Incidence and severity of AEs • Change from baseline in vital signs, clinical laboratory tests, electrocardiograms, and ECOG performance status.
Secondary	
• To evaluate the engraftment of FMT and SER-401 bacteria into the intestinal microbiome community in stool samples. • To assess the association of microbiome study intervention administration with clinical outcomes (objective response rate [ORR], disease control rate [DCR], progression-free survival [PFS] rate, overall survival [OS], and duration of response). • To assess the change in percentage of tumoral CD8 cells in tumor samples in response to anti-PD-1 therapy with or without microbiome study intervention administration.	• Determination of the engraftment of FMT or SER-401 bacteria into each of the microbiome study intervention groups relative to placebo. • ORR: Defined as CR or PR as best response by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 assessment. Participants who do not have RECIST assessment for any reason will be counted as not responding. • DCR: Defined as CR, PR, or stable disease (SD) for ≥ 24 weeks as best response by RECIST v1.1. Participants who do not have RECIST assessment for any reason will be counted as not responding. • PFS: Defined as the time from randomization to date of first documented radiographic progression of disease or date of death due to any cause, whichever occurs first. • PFS rate at 1 year: Defined as the proportion of participants without documented progression of disease or death due to any cause at 1 year. • OS: Defined as the time from randomization until death. • OS rate at 1 year: Defined as the proportion of participants alive at 1 year. • Duration of response: Defined as time from date of documented CR or PR to date of first documented radiographic progression of disease or date of death due to any cause, whichever occurs first.

Objectives	Endpoints
	• Change in the percentage of CD8 cells in tumor tissue from baseline at Cycle 2.
Exploratory	
• To assess the safety and efficacy of SER-401 administration with anti-PD-1 therapy in participants who receive SER-401 after progressing while on placebo. • To evaluate changes in the composition of the fecal microbiome. • To evaluate changes in signatures of host and microbial functional responses in stool and blood. • To explore the association of microbiome, tumor and immune biomarkers in blood, tumor, and stool samples with clinical endpoints and/or AE.	• Incidence and severity of AEs and changes from baseline in vital signs, clinical laboratory tests, electrocardiograms, and ECOG performance status in participants who receive SER-401 after progressing while on placebo. • ORR in participants who receive SER-401 after progressing while on placebo. • DCR in participants who receive SER-401 after progressing while on placebo. • PFS rate at 1 year in participants who receive SER-401 after progressing while on placebo. • OS rate at 1 year in participants who receive SER-401 after progressing while on placebo. • Changes in the composition of the fecal microbiome from baseline to on treatment following administration of FMT, SER-401, or placebo. • Functional changes in transcriptomic, metabolomic, and/or proteomic profiles from baseline to on treatment. • Association of T-cell phenotypic characteristics and immune characteristics in the tumor with clinical outcomes (eg, ORR, DCR, PFS, OS) and/or AEs. • Molecular (genomic, metabolic, and/or proteomic) or microbial biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or mechanism of action of anti-PD-1 therapy and their relationship to microbiome study intervention administration.

AE(s) = adverse event(s); CR = complete response; CTCAE = Common Terminology for Adverse Events; DCR = disease control rate; ECOG = Eastern Cooperative Oncology Group; FMT = fecal microbiota transplant; ORR = objective response rate; OS = overall survival; PD-1 = programmed cell death-1; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 1b, multicenter, randomized, placebo-controlled, blinded study in adult participants with unresectable or metastatic melanoma to evaluate the safety and tolerability of FMT, SER-401, or matching placebo in combination with anti-PD-1 therapy. Participants must have measurable disease that can be biopsied and consent to baseline and on-treatment biopsies.

Approximately 60 participants will be treated with microbiome study intervention or placebo in combination with nivolumab. Enrollment caps will be utilized to ensure adequate representation of participants with low (ie, "unfavorable") fecal microbiome composition of the *Ruminococcaceae* abundance-based metric at screening. Each study intervention (FMT or SER-401) will enroll a minimum of 18 participants (60%) with low *Ruminococcaceae*.

After consenting to participate in this clinical trial, participants will undergo screening for eligibility, including blood and stool biomarker sampling, assessment of stool for the *Ruminococcaceae* abundance-based metric for stratification, and tumor biopsies (baseline and on-treatment core needle or incisional biopsies are required; fine needle aspiration is not acceptable). Participants will be assigned to 1 of the 2 oral microbiome study interventions (FMT or SER-401) by the Investigator based on clinical judgment and availability or feasibility of the interventions. Within each study intervention, participants will be randomized in a 2:1 ratio to the oral microbiome study intervention or matching placebo (Figure 1).

The 2-week antibiotic/microbiome study intervention lead-in phase of the study will consist of 4 days of pretreatment with oral vancomycin (125 mg) or placebo administered 4 times daily (QID), starting on Day -14, followed by a 2 (+1) day washout. The washout may be extended by the additional day, as indicated, if needed to accommodate scheduling. Participants unable to tolerate the antibiotic pretreatment will be discontinued from the study and replaced prior to administration of the microbiome/anti-PD-1 combination.

A 1-week loading regimen of the microbiome study intervention will be performed 2-3 days following antibiotic/placebo administration. Participants assigned to the FMT arm will receive 3 doses of FMT investigational intervention or placebo administered every other day (QOD). If needed to accommodate scheduling, either the second or third dose of FMT (but not both), may be administered with a window of 1 additional day (ie, dosing interval of up to 3 days instead of 2 days). All FMT doses will be dispensed for administration at the study site. The participant should observe a fast of at least 4 hours (no food or drink except for small amounts of water) prior to and 45 minutes after FMT administration.

Participants in the SER-401/placebo arm will receive 7 doses of SER-401 investigational intervention or placebo administered every day (QD) for one week. The first dose of SER-401 or matching placebo will be administered in the clinic and will be followed by a 1-hour observation period after dosing. SER-401 should be taken at approximately the same time on each day and the administration date recorded on the diary card. The participant should observe an overnight or at least a 6-hour fast (no food or drink except for small amounts of water) prior to SER-401 administration. Subsequent doses of SER-401 or matching placebo will be dispensed to the participant for self-administration QD at home.

During the antibiotic/microbiome lead-in phase, participants will use a participant-reported diary to track compliance to the oral antibiotic and SER-401, as well as to record, on a daily basis during administration, the occurrence of solicited symptoms commonly associated with microbiome study intervention (see Section 8.2.5).

Nivolumab therapy will begin on Cycle 1 Day 1, which is approximately one day following the 7-days of lead-in with the microbiome intervention. An anti-PD-1 study intervention cycle will be defined as 4 calendar weeks, starting on the day of each anti-PD-1 infusion. The protocol active treatment phase with anti-PD-1 therapy (nivolumab) will continue for up to 12 cycles, unless the participant experiences confirmed disease progression or unacceptable toxicity in the judgment of the treating physician. Participants will be followed for approximately 2 years from the time of the initiation of study intervention.

Participants assigned to blinded FMT (Group 1) or matching placebo (Group 2) will have 3 clinic visits (QOD) during the antibiotic/microbiome lead-in phase and weekly clinic visits during the microbiome/anti-PD-1 treatment phase for administration of the blinded microbiome study intervention.

Participants assigned to blinded SER-401 (Group 4) or matching placebo (Group 3) will receive enough capsules of the blinded microbiome study intervention to cover administration until the next clinic visit.

Participants will be monitored for safety and will report solicited symptoms using a diary card during the antibiotic and microbiome dosing portions of the trial. Adverse events, including adverse events of special interest (AESIs), will be collected from the start of study intervention until at least 100 days after the last dose of study intervention.

In addition, the first 5 participants enrolled in each microbiome study intervention group (ie, FMT/matching placebo or SER-401/matching placebo) will be contacted twice following the first dose of nivolumab, as follows: once between Days 2 – 4 and once on Day 7 [± 1 day to accommodate weekends or holidays]). The intent of these phone calls is to assess for emerging AEs that may require early intervention.

Blood and stool biomarkers will be collected throughout the study. Participants will be supplied with home fecal collection kits to obtain stool samples for metagenomic and metabolomic analyses. Following randomization, stool will be collected with a window of up to 2 days prior to the following timepoints, when feasible: start of microbiome study intervention (ie, collected after completion of antibiotic/placebo and prior to the start microbiome study intervention) and Cycle 1 Day 1 (ie, 7 days after start of microbiome study intervention). Thereafter, stool will be collected with a window of ± 3 days of the following timepoints, when feasible: Cycle 1 Day 8 (ie, 7 days after first dose of nivolumab); Cycle 2 Day 1; Cycle 3 Day 1; Cycle 4 Day 1 (ie, 4

weeks after last dose of microbiome study intervention); Cycle 7 Day 1; and at the End of Treatment visit.

A screening biopsy is required. An on-treatment tumor biopsy is required when medically feasible. The on-treatment biopsy should occur ideally from the same tumor lesion and after the second dose of anti-PD-1 therapy (ie, Cycle 2, Days 2 – 12); however, any on treatment biopsy will be accepted.

An optional biopsy may be obtained during the course of the study or at the time of disease progression, including from participants who respond and subsequently progress. Participants must provide additional consent for this procedure.

4.1.1 Cross-over for Participants on Placebo in Groups 2 or 3

Participants who were randomly allocated to receive placebo in Groups 2 or 3 and who have radiographic evidence of progression of disease while on study (as described in Section 4.4) will be offered the option to receive active SER-401 and nivolumab treatment as part of a cross-over to Group 5. Participants who agree to this option will provide informed consent and will enter Group 5 following unblinding in the Interactive Web Response System (IWRS). The procedures in Group 5 will be identical to those in Group 4 and need to be repeated according to the Schedule of Activities beginning with the antibiotic administration 14 days prior to Cycle 1.

To be eligible for treatment in Group 5, participants must be unblinded and found to have been assigned to the placebo microbiome intervention arm. Participants must continue to meet all safety-related eligibility criteria described in Section 5.1 and Section 5.2. Additionally, participants must have tolerated nivolumab therapy without unresolved toxicity or toxicity requiring permanent treatment discontinuation as defined in Table 4. A new baseline biopsy is optional and not required for entry into Group 5.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This study is designed to assess the safety and tolerability of treatment with oral microbiome study interventions or matching placebo in enhancing the response to anti-PD-1 therapy in participants with advanced melanoma. The study uses 2 complex, donor-derived products to be tested in combination with anti-PD-1 treatment in adult patients with advanced metastatic melanoma: FMT formulated for oral delivery (Youngster et al., 2016) derived from healthy donors and SER-401, a healthy donor-derived spore composition formulated in capsules for oral administration. The justification for evaluating FMT and SER-401 in separate groups of the same clinical study is that this approach enhances the opportunity to define how the participant microbiome influences CPI therapy by including a wide range of bacterial species from two diverse products. Based on the mechanism of action of improving immune responsiveness to immunotherapy and the lack of antitumor activity of single agent FMT in preclinical tumor

models (Matson et al., 2018), this first in man study is evaluating FMT or SER-401 administration in combination with anti-PD-1 therapy. Donors for each of these products have been selected to have a "favorable" microbiome profile (see Section 2.2.2 and Section 2.2.3) based on the findings of Gopalakrishnan et al. (Gopalakrishnan et al., 2018). In addition to evaluating the safety of these compositions in combination with anti-PD-1 treatment, this study will evaluate the mechanisms by which the microbiome influences immune response and clinical outcomes to CPI treatment.

The study population rationale is provided in Section 2.

4.3 JUSTIFICATION FOR DOSE

Nivolumab will be administered using the established dosing regimen for metastatic melanoma (Section 4.3.1). The dose and schedule proposed for oral FMT (Section 4.3.2) and SER-401 (Section 4.3.3) are based on precedents in other indications and experiences with other bacterial spore products in other clinical trials, respectively.

4.3.1 Rationale for Nivolumab Dose and Schedule

Nivolumab will be administered at a dose of 480 mg Q4W, as approved by the FDA in March 2018 for the treatment of metastatic melanoma (Opdivo USPI, 2019).

4.3.2 Rationale for Oral FMT Dose and Schedule

Oral FMT dose and schedule is guided by historical precedent in other indications; a dose of 10 – 15 capsules is typical in CDI, delivered over 2 consecutive days. As the capsules are large (Size 00, about the size of a multi-vitamin), larger numbers are not considered generally tolerable, and thus, a dose of 10 capsules was selected. Additionally, this dose level (ie, capsule number) and frequency has precedent for chronic oral FMT administration in a clinical trial at Massachusetts General Hospital studying patients with metabolic syndrome (NCT02530385).

4.3.3 Rationale for SER-401 Dose and Schedule

SER-401 dose and schedule are guided by recent experience with another bacterial spore product, SER-287, in a setting of mild-to-moderate ulcerative colitis. In the SERES-101 trial, a 6-day pretreatment antibiotic lead-in with vancomycin 125 mg QID followed by a daily dose of 1 x 10^8 SporQs (equivalent to approximately 1 x 10^7SCFUs) for 8 weeks resulted in significant engraftment of spore species (NCT02618187). Clinical remission, endoscopic improvement, and engraftment was improved with daily dosing compared with weekly dosing. There were no treatment-related drug discontinuations in the SER-287 daily study intervention group, and all treatment-emergent AEs were mild or moderate with no drug-related SAEs. Thus, a similar regimen, 4-day vancomycin 125 mg QID pretreatment antibiotic lead-in followed by daily

SER-401 5×10^6 SCFU for 9 weeks, is proposed for participants with unresectable or metastatic melanoma in the current study.

4.4 TREATMENT BEYOND DISEASE PROGRESSION

Accumulating evidence indicates that a minority of patients treated with immunotherapy may derive clinical benefit from continued treatment despite initial evidence of disease progression (Wolchok et al., 2009). Therefore, participants will be permitted to continue study intervention beyond initial RECIST v1.1-defined disease progression (PD) assessed by the Investigator, provided they meet the following criteria:

- Investigator-assessed clinical benefit
- Participant is tolerating study intervention and has no unresolved toxicity (ie, has returned to baseline grade/severity)
- Participant has a stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, central nervous system metastases)
- Participant agrees to continue treatment beyond progression and has been informed of alternate treatment options as part of the documented informed consent process

All decisions to continue treatment beyond initial progression must be discussed with and agreed upon by the Sponsor and documented in the study records.

A follow-up scan should be performed at the next scheduled imaging evaluation (no sooner than 4 weeks) following initial investigator-assessed progression to determine whether there is evidence of further progressive disease.

If the investigator feels that the participant continues to achieve clinical benefit by continuing treatment, the participant may remain on the trial and continue to receive study intervention(s) and undergo monitoring according to the Schedule of Activities (Section 1.3). Participants should discontinue study intervention upon evidence of further progression, defined as an additional ≥ 10% increase in tumor burden from the time of initial progression (including all target lesions and new measurable lesions).

4.5 END OF STUDY AND END OF TREATMENT DEFINITIONS

Each participant will have an End of Treatment date and an End of Treatment visit. The End of Treatment date is the calendar date when all study interventions are discontinued. The End of Treatment visit is the date that a clinic visit was completed following the last dose of study intervention (ie, after 12 cycles of study intervention or at early discontinuation). All

participants, including those who discontinue early after receiving any study intervention, should have the End of Treatment visit and date to complete the visit procedures. The clinic visit at which disease assessment shows progressive disease may be used as the End of Treatment visit if it occurs 30 (+5) days after the last dose of nivolumab. Every effort should be made to complete the End of Treatment visit within the window; however, the visit should be conducted even if outside the window.

For each participant, the End of Study time point is defined as the date when the last study visit or procedure for that participant occurs.

The End of Study for the study is the date at which the last data point required for statistical analysis or safety follow-up is received from the last participant, whichever occurs later.

5 STUDY POPULATION

Prospective requests for approval of protocol deviations to recruitment and enrollment criteria, also known as waivers or exemptions, are not allowed.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all the following criteria apply:

1. Men and women, ≥ 18 years of age at the time the informed consent is signed.
2. Participant must be willing to provide a baseline stool sample (see Section 8.7.2).
3. Male or female participants of child-producing potential must agree to use contraception or avoidance of pregnancy measures as detailed in Appendix 6 of this protocol during the treatment period and for at least 7 and 5 months, respectively, after the last dose of nivolumab.
4. Women of childbearing potential (as defined in Appendix 6) must have a negative serum pregnancy test within 24 hours prior to the start of study intervention.
5. Participants must be able and willing to comply with the study visit schedule and study procedures and requirements, including the ability to take oral drugs.
6. Histologically-confirmed Stage IV cutaneous melanoma or Stage III cutaneous, acral or mucosal melanoma that is judged inoperable. Participants with a history of uveal melanoma are not eligible.
7. Measurable disease as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1; ie, defined as at least 1 lesion that can be accurately measured in at least 1 dimension [longest diameter to be recorded] with a minimum size of ≥ 10 mm by computerized tomography [CT] scan or caliper measurement on clinical exam or ≥ 20 mm by chest X-ray).
    a. Malignant lymph nodes must be ≥ 15 mm in short axis when assessed by CT scan to be considered pathologically enlarged and measurable.

b. Participants must have at least one measurable lesion by RECIST and a separate lesion amenable to biopsy that has not been previously irradiated.

   i. Participants must be willing to undergo a newly-obtained core needle or incisional biopsy at baseline (prior to antibiotic or antibiotic placebo administration). Fine needle aspiration is not acceptable.

   ii. Participants who have only one measurable lesion per RECIST 1.1 criteria at baseline and no other lesions amendable to biopsy must be discussed with the Medical Monitor prior to enrollment.

8. Participants must be willing to undergo tumor biopsy, ideally from the same tumor location, while on treatment.
9. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
10. Prior radiotherapy must have been completed at least 2 weeks prior to study intervention administration.
11. Screening laboratory values (within 14 days of randomization):
    a. Absolute neutrophil count $\geq 1.0 \times 10^9$/L
    b. Platelets $\geq 100 \times 10^9$/L
    c. Hemoglobin ≥ 9 g/dL
    d. Serum creatinine < 1.5x OR creatinine clearance of at least 40 mL/min
    e. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x upper limit of normal (ULN)
    f. Total bilirubin $\leq 1.5 \times$ ULN
       i. Participants with liver lesions may be eligible if they have total bilirubin ≤ 2.0 x ULN
       ii. Participants with Gilbert's syndrome must have total bilirubin ≤ 3 x ULN and no liver lesions
12. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol, prior to the performance of any protocol-related procedures that are not part of normal care.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

1. Had a surgical procedure requiring general anesthesia less than 2 weeks prior to beginning protocol therapy.
2. Is pregnant, lactating or breastfeeding.
3. Participants who require hemodialysis.

4. Participants with a history of another cancer in the last 5 years, except for: a) curatively resected non-melanoma skin cancer; b) curatively treated cervical carcinoma in situ; c) localized prostate cancer not requiring systemic therapy; and c) other primary tumors with no known active disease present that, in the opinion of the Investigator and the Sponsor, will not affect participant outcome in the setting of the current diagnosis.
5. Any known, untreated brain metastases. Participants with brain metastases are eligible if these have been treated, and provided:
    a. Brain metastases must be stable (image-documented) 4 weeks after completion of treatment for brain metastases and require treatment with less than 10 mg/day prednisone equivalent for at least 2 weeks prior to study intervention administration.
    b. Neurological symptoms should be absent or returned to baseline.
6. Prior checkpoint inhibitor therapy with anti-PD-1 or anti-PD-L1.
    a. Exception: Participants with stage 3 or 4 cutaneous melanoma status post-resection who have received up to one year of **adjuvant** anti-PD-1 therapy who have recurred > 6 months after their last dose of anti-PD-1 therapy are eligible.
7. Other prior systemic treatment (ie, anticancer chemotherapy, immunotherapy, or investigational agents) for unresectable or metastatic melanoma **EXCEPT**:
    a. Participants who received prior BRAF-targeted therapy (ie, BRAF or BRAF-MEK) in the metastatic setting is allowed if the therapy was completed at least 4 weeks prior to the first dose of anti-PD-1.
    b. Participants who received prior anti-CTLA 4 therapy in the **adjuvant** setting are allowed if completed at least 12 weeks prior to the first dose of anti-PD-1.
8. History of active inflammatory bowel disease (eg, active Crohn's disease or ulcerative colitis) with diarrhea OR major gastrointestinal surgery (not including appendectomy or cholecystectomy) within 3 months of enrollment (ie, signed informed consent for the study), OR any history of total colectomy or bariatric surgery (bariatric surgery which does not disrupt the gastrointestinal lumen, ie, restrictive procedures such as banding, are permitted).
9. Any diagnosis of autoimmune disease. Participants with Type I diabetes mellitus, hypothyroidism only requiring hormone replacement, adrenal insufficiency on replacement dose steroids, skin disorders (such as vitiligo, psoriasis or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
    a. Participants with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible.
10. Participants with eczema, psoriasis, lichen simplex chronicus or vitiligo except those with dermatologic manifestations only (eg, participants with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
    a. Participants with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations.

b. Rash must cover less than 10% of body surface area.

c. Disease is well controlled at baseline and only requiring low potency topical steroids (eg, hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%).

d. No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids).

11. Has a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of study intervention administration. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
12. History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (ie, bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest CT scan.
    a. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
13. Has a transplanted organ or has undergone allogeneic bone marrow transplant.
14. Has received a live vaccine within 30 days prior to first dose. Participants must not receive live, attenuated influenza vaccine (eg, FluMist®) within 30 days prior to Cycle 1, Day 1 or at any time during the study and 100 days after last dose of nivolumab.
15. Has used antibiotics within 30 days prior to randomization or has planned or required need for antibiotic prophylaxis for more than 24 consecutive hours during the course of the study.
16. Participants with a history of allergy to study intervention components or history of a severe hypersensitivity reaction to any monoclonal antibody.
17. Known allergy or intolerance to oral vancomycin.
18. Uncontrolled concurrent illness including, but not limited to, ongoing or active infection, clinically significant non-healing or healing wounds, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, significant pulmonary disease (shortness of breath at rest or on mild exertion), uncontrolled infection or psychiatric illness/social situations that would limit compliance with study requirements.

5.3 LIFESTYLE CONSIDERATIONS

No restrictions are required.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure

participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

In this study, stool will be collected at screening for assessment of the fecal microbiome composition of the *Ruminococcaceae* abundance-based metric for stratification. A second screening collection will be allowed if the results of the initial screening collection are indeterminate.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTIONS ADMINISTERED

The study interventions to be administered in this study are summarized in Table 3.

Table 3: Study Intervention

Study Intervention Name	Dosage Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Sourcing
Antibiotic (Vancomycin)	Tablet with microcrystalline cellulose in blinding capsule	125 mg	125 mg	PO	Seres Therapeutics
Matching Placebo for Antibiotic	Microcrystalline cellulose in blinding capsule	0 mg	0 mg	PO	Seres Therapeutics
FMT Capsules	Active glycerol suspension in capsule	$\geq 10^9$ CFU/ 10 capsules	10 capsules	PO	MGH IND 16011
Matching Placebo for FMT Capsules	Placebo glycerol suspension in capsule	0 CFU/ 10 capsules	10 capsules	PO	MGH IND 16011
SER-401 Capsules	Active glycerol suspension in capsule	5 x 10^6 SCFU/ 2 capsules	2 capsules	PO	Seres Therapeutics
Matching Placebo for SER-401 Capsules	Placebo glycerol suspension in capsule	0 SCFU/ 2 capsules	2 capsules	PO	Seres Therapeutics
Nivolumab	Aqueous solution	10 mg/mL	480 mg	IV infusion	Sourced commercially

CFU = colony-forming units; FMT = fecal microbiota transplant; IV = intravenous; MGH = Massachusetts General Hospital; PO = orally; SCFU = spore colony-forming units

Participants will be assigned to receive 1 of the following oral microbiome study interventions (FMT or SER-401) in combination with anti-PD-1 therapy. Within each study intervention, participants will be randomized in a 2:1 ratio to the oral microbiome study intervention or matching placebo:

- FMT or matching placebo will be administered QOD x 3 days during the lead-in phase, followed by QW x 8 weeks during the microbiome/anti-PD-1 treatment phase. The dose of FMT product will be 10 capsules given 3 times for the first week (3 doses), followed 1 time per week for the next 8 weeks (1 dose). This roughly corresponds to 10^9 or more colony forming units (CFU) per 10 capsule dose.
- SER-401 or matching placebo will be administered QD x 7 days during the lead-in phase, followed by QD x 8 weeks during the microbiome/anti-PD-1 treatment phase. The dose per day of SER-401 will be 5 x 10^6 SCFU or 2 capsules.

Prior to initiating the microbiome study intervention, participants will undergo a 4-day lead-in pretreatment with either antibiotic (vancomycin) or antibiotic placebo, depending on group randomization assignment, to prime the gut microbiome for engraftment of the oral microbiome study intervention, which will be administered following a 2-3 day washout. Participants unable to tolerate the antibiotic pretreatment will be discontinued from the study and replaced.

Administration of study intervention will be staggered by at least 1 day for the first 5 participants enrolled in each microbiome study intervention group (ie, FMT/matching placebo or SER-401/matching placebo) to monitor for safety.

The protocol active treatment with anti-PD-1 therapy (nivolumab, 480 mg) will be administered intravenously (IV) according to institutional guidelines Q4W for up to 12 cycles, unless the participant experiences confirmed disease progression or unacceptable toxicity in the judgment of the treating physician. A cycle is defined as 4 calendar weeks.

Study intervention administered by site personnel will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

The study intervention administered in this protocol is for investigational use only.

All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff. Storage requirements for the study intervention are as follows:

- Vancomycin study intervention and matching placebo should be stored at room temperature for both clinical site storage, as well as at-home use.

- FMT study intervention and matching placebo must be stored at ≤ -65°C at the clinical site.
- SER-401 study intervention and matching placebo must be stored at ≤ -15 °C at the clinical site and refrigerated at 2°C to 8°C during at-home use.
- Nivolumab must be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing.

The Investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may dispense and/or administer study intervention. In this study, oral study intervention, including vancomycin and oral microbiome study intervention, will be dispensed to the participant for self-administration.

Participants should return any unused study drug to the site at their next study visit. Returned study intervention should not be re-dispensed to other participants. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused or returned study interventions are provided in the Pharmacy Manual.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 Intervention Assignment

Assignment to 1 of the 2 microbiome study interventions will be made by the Investigator based on clinical judgment and availability or feasibility of the interventions. All participants will be randomly allocated (in a 2:1 ratio) to the oral microbiome study intervention or placebo within the 2 microbiome study interventions using an Interactive Web Response System (IWRS). Before the study is initiated, log in information and directions for the IWRS will be provided to each site.

Randomization will be stratified by fecal microbiome composition of *Ruminococcaceae* at screening (see Section 2.2.2): high (ie, “favorable”) vs low (ie, “unfavorable”). Each study intervention (FMT or SER-401) will enroll a minimum of 18 participants (60%) with low *Ruminococcaceae*.

6.3.2 Blinding

Within the 2 microbiome study interventions, participants will be randomly assigned in a 2:1 ratio to the oral microbiome study intervention or matching placebo. Nivolumab will be administered open-label as standard of care to all groups. Investigators, site personnel, and participants will remain blinded to the assignment of microbiome study intervention throughout the course of the study. Select Sponsor personnel, including but not limited to the Medical Monitor, Clinical Scientists, Biostatistician, and Patient Safety, will be unblinded to treatment assignment for ongoing safety monitoring.

6.3.3 Unblinding

The IWRS will be programmed to accommodate unblinding and cross-over cases. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Medical Monitor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

If a participant has radiographic evidence of progression of disease while on study (see Section 4.4), the Investigator will be able to unblind the participant's intervention assignment. If the participant was allocated to one of the placebo groups (Group 2 or Group 3), the participant will be offered the option to receive active SER-401 and nivolumab treatment (Group 5). The study intervention (active SER-401 and nivolumab) will be offered open label; Investigators, site personnel, and participants will be unblinded to study intervention administered in Group 5.

6.4 STUDY INTERVENTION COMPLIANCE

Participant compliance with study intervention will be assessed at each visit. Compliance for study intervention administered by site personnel will be assessed using site drug accountability records. Study intervention that is self-administered by the participant will be tracked by the participant using a participant-reported diary and reconciled with any returned study intervention.

For study medication self-administered by the participant at home, missed doses should be taken as soon as the participant remembers the missed dose. However, if it is almost time for the next dose, the missed dose should be skipped, and the regular dosing schedule should be followed. The participant should not take a double dose to make up for a missed dose.

Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

6.5 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, probiotics, and/or herbal supplements) that the participant is receiving at the time of enrollment through at least 100 days post last dose of study intervention must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Permitted Therapy

Concomitant medications or treatments (eg, acetaminophen/paracetamol, diphenhydramine) may be prescribed if considered necessary for adequate prophylactic or supportive care except for those medications identified as "excluded" in Section 5.2.

6.5.2 Cautionary Therapy

Participants with planned or required antibiotic prophylaxis for more than 24 consecutive hours during the course of the study should not be enrolled. Once enrolled, if the need for antibiotic treatment arises, the decision to continue the participant will be at the discretion of the Investigator, after discussion and agreement with the Medical Monitor.

6.5.3 Prohibited Therapy

The medications listed below are prohibited during the study. The Sponsor must be notified if a participant receives any of these during the study.

- Any concurrent investigational anticancer therapy.
- Immunosuppressive medications, including chronic systemic steroids at physiologic doses (equivalent to a dose > 10 mg oral prednisone), 14 days prior to the first dose of antibiotic treatment (except for participants who require hormone replacement therapy [HRT] such as hydrocortisone). A temporary course of steroids (ie, contrast allergy, chronic obstructive pulmonary disease) may be permitted, depending on the duration and dose, after discussion and agreement with the Medical Monitor.
- Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic, or hormonal treatment.

- Any live attenuated vaccine therapies used for the prevention of infectious diseases (for up to 30 days prior to the first dose of antibiotic treatment and 100 days after the last dose of study intervention), including for influenza (eg, FluMist), for up to 30 days prior to the first dose of nivolumab and 100 days after the last dose of study intervention.
- Herbal and natural remedies, including probiotics, unless discussed and agreed with the Medical Monitor.

6.6 DOSE MODIFICATIONS

Immuno-oncology agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms (Opdivo Immune-Mediated Adverse Reactions Management Guide, 2019) have been developed to assist Investigators in assessing and managing the following groups of drug-related AEs:

- Immune-mediated colitis
- Immune-mediated hepatitis
- Immune-mediated endocrinopathies (hypophysitis, adrenal insufficiency, hypothyroidism and hyperthyroidism, Type 1 diabetes mellitus)
- Immune-mediated skin adverse reactions
- Immune-mediated encephalitis
- Immune-mediated pneumonitis
- Immune-mediated nephritis and renal dysfunction
- Other immune-mediated AEs

Based on the available characterization of the mechanism of action, and preliminary data from ongoing studies, nivolumab may cause AEs similar to, but independent of, concurrent therapy, may exacerbate the frequency or severity, or may have non-overlapping toxicities. The anticipated important safety risks are outlined below. Refer to the approved prescribing information for nivolumab for a complete summary of safety information (Opdivo USPI, 2019).

6.6.1 Dose Reductions of Study Intervention

There will be no dose escalations or dose reductions to any of the study interventions.

Dose administration timing may be held or delayed according to Section 6.6.2.

6.6.2 Dose Delays or Discontinuations Due to Toxicity

Participants who experience an AE described in Table 4 will be discontinued from all study interventions and should continue follow-up assessments as outlined in the Schedule of Activities.

Grade 3 and 4 toxicities are observed in all trials of nivolumab in multiple tumor types. As such toxicities are anticipated; monitoring for AEs described in Table 4 will continue throughout the study.

The Investigator may attribute each AE to the antibiotic, combination of nivolumab and oral microbiome study intervention, or to nivolumab or oral microbiome study intervention alone. Study participants may not have any dose reductions of vancomycin, nivolumab or oral microbiome study intervention in this study. If toxicity does not resolve or the criteria for resuming study intervention are not met, the participant must be discontinued from the study intervention.

Holding of 1 study intervention and not the other study intervention(s) is appropriate if, in the opinion of the Investigator, the toxicity is clearly related to 1 of the study interventions. Appropriate documentation is required regarding the drug to which study intervention the Investigator is attributing the AE. If, in the opinion of the Investigator, the toxicity is related to a combination of 2 study interventions, then all drugs should be held according to recommended dose modifications.

Specific anticipated or potential toxicities associated with the administration of nivolumab or oral microbiome study intervention, as well as the measures intended to avoid or minimize such toxicity in this trial, are described in the following sections. Guidance with respect to the individual study intervention is provided in Section 6.6.3 and Section 6.6.1, respectively.

Dose delays and interruptions are permitted for toxicity reasons (see Section 6.6.1 and Section 6.6.3). Dose delays and interruptions for reasons other than toxicity, such as surgical procedures, may be allowed with Medical Monitor approval. The acceptable length of interruption will depend on agreement between Investigator and Medical Monitor, but in general should not exceed 6 weeks.

Refer to the approved prescribing information nivolumab (Opdivo USPI, 2019), vancomycin (Vancocin USPI, 2018), and the Investigator's Brochures for FMT and SER-401 for complete summaries of safety information.

Table 4: Toxicity Criteria Requiring Permanent Treatment Discontinuation From Nivolumab or Microbiome Interventions

Participants should be monitored for the occurrence of any of the following AEs that are considered by the Investigator to be related (ie, possibly, probably, or definitely related) to nivolumab, microbiome study intervention, or the combination of nivolumab and microbiome study intervention. Treatment with all study intervention should be permanently discontinued for the following:
• Any Grade 2 uveitis or eye pain or blurred vision related to study intervention that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment • Any Grade 3 non-skin AE related to study intervention lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, study intervention-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, infusion reactions, and endocrinopathies: o Grade 3 study intervention-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, myocarditis, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation o Grade 3 study intervention-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement. o Grade 3 laboratory abnormalities related to study intervention do not require discontinuation, except: ▪ Grade 3 thrombocytopenia related to study intervention lasting > 7 days or associated with bleeding requires discontinuation ▪ Any liver function test abnormality related to study intervention meeting the following criteria requires discontinuation: – Grade ≥ 3 AST or ALT (> 5 x ULN), unless a possible favorable benefit/risk warrants continuation and a discussion between the Investigator and Medical Monitor occurs – Grade ≥ 3 total bilirubin (> 3 x ULN), unless a possible favorable benefit/risk warrants continuation and a discussion between the Investigator and Medical Monitor occurs – Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN • Any Grade 4 AEs or laboratory abnormalities (including but not limited to creatinine, AST, ALT, or total bilirubin) related to study intervention, except for the following events that do not require discontinuation: o Grade 4 neutropenia ≤ 7 days o Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase o Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset o Grade 4 endocrinopathy AEs related to study intervention, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Medical Monitor. • Any AE, laboratory abnormality, or intercurrent illness, which in the judgment of the Investigator presents a substantial clinical risk to the participant with continued administration of study intervention • Any infection with an organism acquired from FMT or SER-401.

AE(s) = adverse event(s); ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

6.6.2.1 Potential for Overlapping Toxicities with Nivolumab and Oral Microbiome Study Intervention

Adverse events commonly associated with microbiome study intervention include: fever; nausea, diarrhea, vomiting, abdominal discomfort, constipation, and flatulence. Among these AEs, diarrhea and nausea have been reported in ≥ 10% of patients receiving nivolumab monotherapy

and are most likely to have the potential to overlap when nivolumab and oral microbiome study intervention are administered together. The remaining AEs have been reported with nivolumab monotherapy, but at a lower incidence (ie, < 10%), and thus, are less likely to overlap.

6.6.3 Dose Modifications for Nivolumab

Specific anticipated or potential toxicities associated with the administration of nivolumab, as well as the measures taken intended to avoid or minimize such toxicity in this trial, are described in the following table and sections.

This study will include set dosing for nivolumab (480 mg Q4W). No dose escalations or reductions of nivolumab are allowed. If toxicity does not resolve or the criteria for resuming study intervention are not met within 6 weeks (ie, 42 days), the participant must discontinue nivolumab.

Specific anticipated or potential toxicities associated with the administration of nivolumab, as well as the measures to be taken to avoid or minimize such toxicity in this trial, are described in Table 5.

AEs associated with nivolumab exposure may represent an immunologic etiology. These immune-related adverse events (irAEs) may occur shortly after the first dose or several months after the last dose of treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, drug-related AEs have included pulmonary toxicity, renal toxicity (including acute renal failure), endocrine abnormalities, GI toxicity, dermatologic toxicity (including rash), and hepatotoxicity. For nivolumab monotherapy, as well as when administered in combination, the majority of these AEs have been managed successfully with supportive care and, in more severe cases, a combination of dose delay, permanent discontinuation, and/or use of corticosteroids or hormone replacement therapy (endocrinopathies). For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, and skin biopsy may be included as part of the evaluation.

Dose modification and toxicity management guidelines for irAEs associated with nivolumab are provided in Table 5.

Table 5: Dose Modifications and Toxicity Management Guidelines for Adverse Events Specific to Nivolumab

Adverse Reaction	Severity[a]	Dose Modifications
Colitis	Grade 2 diarrhea or colitis	Withhold dose[b]
	Grade 3 diarrhea or colitis	Withhold dose[b] when administered as a single agent
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose[b]
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hepatitis/non-HCC	AST or ALT more than 3 and up to 5 times the ULN or total bilirubin more than 1.5 and up to 3 times the ULN	Withhold dose[b]
	AST or ALT more than 5 times the ULN or total bilirubin more than 3 times the ULN	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose[b]
	Grade 4 hypophysitis	Permanently discontinue
Adrenal insufficiency	Grade 2 adrenal insufficiency	Withhold dose[b]
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Type 1 diabetes mellitus	Grade 3 hyperglycemia	Withhold dose[b]
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and renal dysfunction	Serum creatinine more than 1.5 and up to 6 times the ULN	Withhold dose[b]
	Serum creatinine more than 6 times the ULN	Permanently discontinue
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose[b]
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue
Encephalitis	New onset moderate or severe neurologic signs or symptoms	Withhold dose[b]
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction • First occurrence • Recurrence of the same Grade 3 adverse reaction	Withhold dose[b] Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Grade 3 myocarditis	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

Source: Opdivo USPI, 2019

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HCC = hepatocellular carcinoma; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; ULN = upper limit of normal

[a] Guidelines based on toxicity graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (NCI CTCAE v4).

[b] Resume treatment when adverse reaction improves to Grade 0 or 1.

[c] Resume treatment when AST/ALT return(s) to baseline.

6.6.3.1 Dose Modifications and Toxicity Management for Infusion-related Reaction Associated with Nivolumab

Interrupt or slow the rate of infusion in participants with mild or moderate infusion reactions. Discontinue nivolumab in participants with severe or life-threatening infusion reactions.

All Grade 3 or 4 infusion reactions must be reported within 24 hours to the study Medical Monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded as described in Section 10.5.3.

Dose modification and toxicity management guidelines for infusion-related reactions are provided in Table 6.

Table 6: Dose Modification and Toxicity Management Guidelines for Infusion-related Reaction Associated with Nivolumab

Grade (NCI CTCAE v 5.0)	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Remain at bedside and monitor participant until recovery from symptoms.	The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion** Begin an IV infusion of normal saline and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further study medication will be administered at that visit.	For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening consequences; urgent intervention indicated	**Stop Infusion** Begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the Investigator is comfortable that the symptoms will not recur. Remain at bedside and monitor participant until recovery of the symptoms. **Study drug will be permanently discontinued.** Investigators should follow their institutional guidelines for the treatment of anaphylaxis.	No subsequent dosing
In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).		
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.		

For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov

CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; NSAIDs = nonsteroidal anti-inflammatory drugs; IV = intravenous

6.6.3.2 Management of Invasive Infections

Potential AESIs include invasive infections (eg, bacteremia, abscess, meningitis). Among 286 subjects enrolled in completed studies conducted by Seres Therapeutics who have received a microbiome investigational drug, a single event of invasive infection (moderate submental abscess unrelated to microbiome investigational drug) has been reported. Notable findings of the report include: the subject had a prior history of a dental infection; and at the time of the report, the subject did not experience fever, swelling, warmth, erythema, or enlarged or tender lymph nodes. The submental abscess, diagnosed by an Ear, Nose, and Throat examination, resolved following treatment with broad spectrum antibiotics.

The protocol monitors such toxicities (see Appendix 5). All SAEs and AESIs will be collected and reported as described in Section 8.3.1.

Participants who develop an invasive infection should be managed according to institutional guidelines.

A study-wide hold and evaluation by the DMC will be initiated if, 1) any SAE or AESI considered by the Investigator to be related to FMT or SER-401 occurs, or 2) any infection with an organism acquired from FMT or SER-401 occurs in any participant during the study. Microbiologic testing for both aerobic and anaerobic organisms will be requested to assess whether the infection is likely related due to an organism acquired from FMT or SER-401. Any isolates obtained should be retained for genomic sequencing.

6.7 INTERVENTION AFTER THE END OF THE STUDY

There will be no study intervention provided following the end of the study.

7 DISCONTINUATIONS OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Participants must discontinue study intervention if they experience any of the following:

- Any toxicity described in Table 4
- Intolerable toxicity related to study intervention, including the development of an AE determined by the Investigator to be unacceptable even with the participant's potential response to intervention due to the severity of the event
- Any dosing interruption lasting > 6 weeks with the following exceptions:
  - Dosing interruptions to allow for prolonged steroid tapers to manage AEs related to study intervention
  - Dosing interruptions > 6 weeks for AEs unrelated to study intervention may be allowed if approved by the Medical Monitor

- Any medical condition that may jeopardize participant safety if he or she continues to receive study intervention
- Use of another anticancer therapy
- Pregnancy (see Appendix 6)
- Symptomatic deterioration attributed to disease progression
- Progression of disease: Either unequivocal symptomatic progression necessitating a change in therapy in the opinion of the treating physician or confirmed radiographic progression as defined by cross-sectional imaging utilizing RECIST v1.1 criteria (see Appendix 3)

Participants have the right to voluntarily withdraw from study intervention at any time for any reason. In addition, the Investigator has the right to withdraw a participant from study intervention at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Investigator or Sponsor determines it is in the best interest of the participant
- Participant noncompliance

The primary reason for study intervention discontinuation should be documented on the appropriate eCRF page.

The visit at which disease assessment shows progressive disease may be used as the treatment discontinuation visit if it occurs 30 (+5) days after the last dose of nivolumab; participants who discontinue study intervention for any reason other than PD or loss of clinical benefit should have an end of treatment discontinuation assessment as outlined in the Schedule of Activities (SOA; see Section 1.3). All participants should to continue follow-up assessments as outlined in the SOA (Section 1.3). Additionally, participants who have received any microbiome study intervention should continue to be followed for SAEs and AESIs up to 26 weeks after the last dose of microbiome study intervention (see Section 8.3.1).

7.1.1 Study-wide Hold for Specified Safety Events

A study-wide hold and evaluation by the study DMC will be initiated if, 1) any SAE or AESI considered by the Investigator to be related to FMT or SER-401 occurs, or 2) any infection with an organism acquired from FMT or SER-401 occurs in any participant during the study. All study participants will immediately discontinue administration of the oral microbiome study intervention but may continue to receive nivolumab should one of these events occur. In addition, further enrollment of new participants into the study will be suspended until the event is adjudicated by the Data Monitoring Committee (see Section 9.5.1).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM STUDY

When study intervention is discontinued, participants should have an end of treatment discontinuation assessment followed up by assessment 100 days post last dose as outlined in the SOA (see Section 1.3). Information on survival follow-up will be collected for every 3 months for approximately 2 years from the initiation of study intervention until any of the following occurs:

- Death
- Lost to follow-up
- Study termination by the Sponsor
- Participant requests to be withdrawn from follow-up
- Investigator requests that the participant is withdrawn from follow-up

A participant may withdraw a consent at any time and discontinue study intervention and further participation on the study. This request must be documented in the source documents and signed by the Investigator. The Sponsor may retain and continue to use any data collected before such withdrawal of consent. Participants who withdraw consent will not be followed for any reason after consent has been withdrawn. However, the study staff may use a public information source (eg, county records) to obtain information about survival status only.

Other reasons for discontinuation of study intervention and/or participation in a follow-up phase of the study may include death, adverse events, physician decision, protocol deviation, eligibility not met, progressive disease. A participant is considered to have completed the study if he/she has completed all phases of the study, including the antibiotic/microbiome lead-in phase, the microbiome/anti-PD-1 phase, the anti-PD-1 phase, and the safety and survival follow-up.

The primary reason for treatment and study discontinuation are documented on the appropriate eCRF page.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit

schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

Please see Section 1.3 for the schedule of activities to be performed during the study. All activities must be performed and documented for each participant in the order of schedule of activities. Participants will be closely monitored for safety and tolerability throughout the study. Participants should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable as deemed by the Principal Investigator (PI).

If the timing of a protocol-mandated study visit coincides with the holiday, weekend, or other administrative disruption that precludes the visit, the visit should be scheduled on the nearest following feasible date. The time between nivolumab doses must not be less than 25 days. Refer to the Schedule of Activities (Section 1.3) for visit windows.

Collection of any non-safety-related data or participant samples may be terminated by the Sponsor at any time if further collection of such data or samples is also not related to the study's primary or secondary objectives. The decision to discontinue any data collection will be communicated to the sites and Institutional Review Board/Independent Ethics Committee (IRB/IEC) by means of a memorandum and will not require a protocol amendment.

8.1 EFFICACY ASSESSMENTS

Participants will undergo tumor assessments as designated in the schedule of activities (see Section 1.3) regardless of dose delays, until loss of clinical benefit as determined by the Investigator (unless the participant withdraws consent or the Sponsor terminates the study). All participants who discontinue study intervention for reasons other than disease progression (eg, AEs) will continue tumor assessments for up to 1 year from initiation of nivolumab treatment or until study completion, death, disease progression, initiation of another systemic anticancer therapy, loss to follow-up, withdrawal of consent, or study termination, whichever occurs first. At the Investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

Measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to randomization do not have to be repeated at screening

Screening assessments must include CT scans (with IV contrast unless contraindicated and oral contrast as appropriate per institutional standards) of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (ie, in participants with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed, and MRI scans may be performed. If the participant has a known history of brain metastases or is symptomatic in the opinion of the Investigator, scans of the head should be obtained.

If a CT scan for a tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full contrast diagnostic CT scans.

Bone scans (technetium-99m [TC-99m]) should be performed at screening if clinically indicated. If bone metastases are present at screen and cannot be seen on CT or MRI scans, or if clinically indicated, TC-99m bone scan should be repeated when complete response (CR) is identified in target disease or when progression in bone is suspected.

CT scans of the neck or extremities should also be performed if clinically indicated and repeated throughout the study if there is evidence of disease at screening.

All measurable and evaluable lesions should be reassessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (eg, same contrast protocol for CT scans).

Response will be assessed by the Investigator using RECIST v1.1 (see Appendix 3). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the Investigator before dosing at the next cycle.

8.2 SAFETY ASSESSMENTS

Safety assessments will consist of monitoring and recording AEs, including serious adverse events (SAEs) and adverse events of special interest (AESIs), performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study. Planned timing for all safety assessments is provided in the schedule of activities (Section 1.3).

Certain types of events require immediate reporting to the Sponsor, as described in Section 8.3.1.1.

8.2.1 Medical History and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including, stage, date of diagnoses, and prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol, and drugs of abuse, will be recorded at baseline. In addition, all medications (eg, prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, probiotics, nutritional supplements, FMT) used by the participant within 28 days prior to initiation of study intervention will be recorded. Demographic data may include age, sex, and race/ethnicity.

8.2.2 Physical Examinations

A complete physical examination should be performed at screening and should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the Medical History eCRF page.

ECOG Performance Status (see Appendix 2) should be assessed per the schedule of activities in Section 1.3.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF page.

8.2.3 Vital Signs

Vital signs should include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, pulse oximetry (required only at screening), and temperature and should be collected as outlined in the Schedule of Activities (Section 1.3). Vital signs collected at the screening visit should be recorded on the appropriate eCRF. For each visit thereafter, only vital signs obtained prior to the study intervention administration as outlined in the Schedule of Activities or during an AE (eg, temperature or event of fever) should be recorded on the eCRF. All vital signs collected per protocol should be documented in the participant's medical record.

Vital signs should be measured within 15 minutes prior to and after the administration of nivolumab (see Section 6). Vital signs may be measured, if medically indicated, at other time points.

8.2.4 Electrocardiograms

Single electrocardiogram (ECG) recordings will be obtained at specified time points, as outlined in the Schedule of Activities (Section 1.3), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using an institutionally-approved ECG. Lead placement should be as consistent as possible. ECG recordings should be performed after the participant has been resting in a supine position for at least 10 minutes.

For safety monitoring purposes, the Investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the participant's permanent study file at the site. The investigator's assessment (ie, normal, abnormal [not clinically significant], or abnormal [clinically significant]) should be recorded on the appropriate eCRF.

8.2.5 Participant Diary

Participants will complete a paper diary to track compliance to the self-administered oral antibiotic and microbiome interventions throughout the study and to record the occurrence of solicited symptoms commonly associated with microbiome study intervention. Symptoms collected include: gas or flatulence; abdominal discomfort (distention, bloating, pain or cramping); diarrhea; vomiting; constipation, and oral temperature. Symptoms will be tracked on a daily basis from the start of the study intervention administration through the end of Cycle 2 using a paper diary card (Appendix 8). Participants will be asked to bring this diary to each clinical visit so that the staff can discuss the compliance and safety information with the participant. After discussion with the participant, should the Investigator determine a symptom is on an AE, the event should be documented in the medical records and on his/her eCRF, as appropriate.

8.2.6 Clinical Safety Laboratory Assessments

Clinical laboratory tests will be performed as described in the Schedule of Activities (Section 1.3).

The Investigator must review the laboratory report, document this review, and designate results as being not clinically significant or clinically significant. Clinically significant abnormal laboratory findings include those are those for which an action was taken (ie, providing fluid, transfusion, medication, and/or holding, delaying, or discontinuing study intervention) or those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. Clinically significant changes occurring during the study should be documented on the appropriate eCRF. The laboratory reports must be filed with the source documents.

In the event of a Grade 3 or Grade 4 laboratory toxicity, the test for the abnormal laboratory value should be repeated until the event is resolved to ≥ Grade 1 or baseline.

8.2.6.1 Local Laboratory Assessments

Samples for the laboratory tests in Table 7 will be sent to the study site local laboratory for analysis:

Table 7: Laboratory Tests Sent to the Study Site Local Laboratory for Analysis

Profile	Laboratory Test
Hematology	CBC, including WBC count RBC count hemoglobin hematocrit platelet count differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), if clinically indicated
Chemistry Panel (Serum or Plasma)	sodium potassium magnesium chloride bicarbonate glucose BUN or urea creatinine total protein albumin phosphorus calcium total bilirubin alkaline phosphatase ALT AST LDH TSH (T3 and FT4 should be checked if TSH is outside the normal range)
Urinalysis	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; LDH = lactate dehydrogenase; RBC = red blood cell; TSH = thyroid-stimulating hormone; WBC = white blood cell

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or SAE can be found in Appendix 5.

Investigators will seek information on AEs at each participant contact. Symptoms reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), including those captured on the participant diary, or those noted by study personnel should be assessed by the Investigator according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. If the event meets

the definition of an AE, it should be recorded in the participant's medical record and on the Adverse Event eCRF page, as appropriate.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, AESI, or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Appendix 5).

8.3.1 Time Period and Frequency for Collecting AE, AESI, SAE, and Other Reportable Safety Event Information

All SAEs will be collected from the time the participant signs informed consent until at least 100 days after the last dose of nivolumab. However, in the case of early discontinuation, participants should be followed for SAEs for up to 26 weeks after the last dose of microbiome study intervention.

All AEs, including AESIs, will be collected from the start of study intervention until at least 100 days after the last dose of study intervention. However, in the case of early discontinuation, participants should be followed for AESIs for up to 26 weeks after the last dose of microbiome study intervention.

Prior to initiation of study intervention, only SAEs that are-related to a protocol-mandated intervention, including those that occur prior to the assignment of study procedures (eg, screening invasive procedures, such as biopsies) should be reported. After obtaining informed consent, but prior to initiation of study intervention, other medical occurrences will be recorded as medical history.

If the Investigator learns of any SAE, including a death, at any time after the end of the AE reporting period, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor or its designee. The Investigator should report these events directly to the Sponsor or its designee, either by faxing or emailing the SAE report form.

The method of recording and reporting AE, AESI, and SAE are provided in Appendix 5. The procedure for submitting SAE reports is provided in Section 8.3.8.2.

During the 9-week microbiome study intervention administration, participants will use a participant-reported diary to record, on a daily basis during administration, the occurrence of solicited symptoms commonly associated with microbiome study intervention. For this study, solicited symptoms include: gas or flatulence; abdominal discomfort (distention, bloating, pain or cramping); diarrhea; vomiting; and constipation.

The method of reporting all deaths are provided in Appendix 5.

8.3.1.1 Events Requiring Expedited Reporting to the Sponsor

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The Investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the Investigator becomes aware of the event. The following is a list of events that the Investigator must report to the Sponsor within 24 hours of becoming aware of the event, regardless of relationship to study intervention:

- All SAEs (defined in Appendix 5)
- Protocol-specified AEs of special interest (defined in Section 8.3.7)
- Pregnancy (see Section 8.3.5 for details on reporting requirements)
- Occurrence of overdose (see Section 8.4 for details on reporting requirements)

8.3.2 Follow-up Event Reporting

The Investigator must report new significant follow-up information for these events to the Sponsor immediately (ie, no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and AEs of special interest (as defined in Section 8.3.7) will be followed through at least 100 days post-last dose of study intervention, until event resolution or death, the participant is lost to follow-up (as defined in Section 7.3), or the participant withdraws consent. Further information on follow-up procedures is provided in Appendix 5.

For SAEs and AEs of special interest, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (eg, from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

8.3.3 Method of Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for discussion of symptoms and eliciting AE information at all participant evaluation time points. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences including symptoms reported on the diary cards. Examples of non-directive questions include: “How have you felt since your last clinic visit?”, “Have you had any new or changed health problems since you were last here?”

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met (see Section 8.3.1.1). Investigators must also comply with local requirements for reporting SAEs to the IRB/IEC or other local health authorities.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, Investigators, and drug manufacturer(s).

Expectedness will be assessed using the Investigator Brochure(s) as reference documents. Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives specific safety-related information (eg, SUSAR notification; summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator’s Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until at least 7 (female partners of male participants) and 5 (female participants) months after the last dose of nivolumab. Female participants, as well as female partners of male participants, of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 5 or 7 months, respectively, after the last dose of nivolumab. If a pregnancy is reported,

the Investigator should inform the Sponsor within 24 hours of becoming aware of the pregnancy and should follow the procedures outlined in Appendix 6. Abnormal pregnancy outcomes that meet serious criteria (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

A clinical trial specific Pregnancy Reporting form should be completed and submitted immediately to the Sponsor or its designee, either by faxing or by scanning and emailing the form using the fax number or email address provided to Investigators (see Section 8.3.8.2). Pregnancy should not be recorded on the Adverse Event eCRF page. The Investigator should discontinue study intervention and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (eg, an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the SAE report form. In addition, the Investigator will submit an updated clinical trial specific Pregnancy Reporting form when updated information on the course and outcome of the pregnancy becomes available.

8.3.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Progression of the cancer under study, as judged by the Investigator, is not considered a reportable event. If upon further review by the Investigator, the event is determined as not being associated with underlying progression of disease, it must be reported as an SAE within 24 hours to the Parker Institute for Cancer Immunotherapy Pharmacovigilance Group as described in Section 8.3.8.2.

8.3.7 Adverse Events of Special Interest

Selected non-serious and serious AEs, known as adverse events of special interest (AESIs), are those of scientific and medical concern specific to the product or program for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is appropriate.

Adverse events of special interest for this trial include:

- An invasive infection (eg, bacteremia, abscess, meningitis) at least possibly related to FMT or SER-401 interventions. Microbiologic testing should be performed, if possible, to assess whether the infection is due to an organism acquired from FMT or SER-401.

All AEs and AEs of special interest will be collected and reported according to Section 8.3.1. Serious AESIs will be adjudicated by the DMC.

8.3.8 Sponsor Contact Information

8.3.8.1 Emergency Medical Contacts

Parker Institute for Cancer Immunotherapy Medical Monitor Contact Information:

Medical Monitor: Marko Spasic, MD

Parker Institute for Cancer Immunotherapy
1 Letterman Drive, Ste. D3500
San Francisco, CA 94080
mspasic@parkerici.org

Telephone No.: (415) 539-3165 (Office; United States)

8.3.8.2 Safety Reporting Contacts

The following contact information should be used when submitting safety-related paper forms (SAE report form and Pregnancy Report Form) as described in Appendix 5 for SAEs and other reportable safety events. These forms should be completed and submitted to the Sponsor immediately (ie, no more than 24 hours after becoming aware of the event), by faxing to the Parker Institute for Cancer Immunotherapy Pharmacovigilance Group at: 415-610-5471 within 24 hours of event awareness. If technical issues arise, please contact Parker Institute for Cancer Immunotherapy Pharmacovigilance Group immediately at 415-930-4414, and the form may be scanned and emailed to safety@parkerici.org.

Parker Institute for Cancer Immunotherapy Pharmacovigilance Group:

- Pharmacovigilance Fax Number: 415-610-5471
- Pharmacovigilance email: safety@parkerici.org
- Pharmacovigilance Telephone Number: 415-930-4414

8.4 TREATMENT OF OVERDOSE

Overdose is defined as any dose higher than the dose specified to be administered in accordance with the protocol.

The Investigator must immediately notify the Parker Institute for Cancer Immunotherapy Pharmacovigilance Group of any occurrence of overdose with study intervention.

All overdoses should be reported as an SAE with the safety criteria of "**other important medical event**." Details of signs and symptoms, clinical management, and outcome should be reported, if applicable. Overdoses should also be captured as protocol deviations.

The PI has the obligation to report the deviations to the IRB/IEC.

8.5 PHARMACOKINETICS

Pharmacokinetic parameters are not evaluated in this study.

8.6 ANTI-DRUG ANTIBODIES

Antibodies to nivolumab are not evaluated in this study.

8.7 BIOMARKERS

The secondary biomarker objective of this study is to determine the engraftment of FMT and SER-401 bacteria into the intestinal microbiome community in stool samples and if the percentage of tumoral CD8 cells changes from baseline (prior to antibiotic treatment) in response to microbiome administration and nivolumab treatment. Engraftment will be determined by evaluation of baseline and on treatment stool samples using deoxyribonucleic acid (DNA) sequencing and a comparison to the stool samples from the placebo group. An engrafting species is defined as any species which is detectable in the microbiome intervention, absent in the participant at baseline, and present in the participant at any time point after treatment initiation. The number of engrafting species will be summarized by participant, study intervention group, and time point.

The composition of the GI microbiome of participants will be characterized using genomic data sets generated from stool. Genomic data sets will define the bacterial composition of the microbiome of a participant at a given time point and relative to baseline. Genomic sequence read data sets will be analyzed to assign a taxonomic identity at the resolution of an operational taxonomic unit (OTU) and, further, to define the relative proportion of each OTU to all other OTUs in a given sample. Changes in the composition of the fecal microbiome will be measured in terms of both the total number of unique types of bacteria (ie, α-diversity) and the microbial composition (ie, β-diversity). The composition of other constituents of the microbiome such as fungi and viruses in the stool may be characterized.

Non-parametric and machine learning computational methods will be applied to the genomic datasets to characterize a participant's GI tract post-treatment compared to baseline.

Differences between changes in the microbiome across the various study intervention groups will be evaluated in terms of changes in α-diversity, β-diversity, and the prevalence and relative abundance of specific OTUs.

The percentage of tumoral CD8 cells will be determined from tumor tissue using immunohistochemistry (IHC). Tumor biopsies at baseline and on-treatment will be assessed for the percentage of tumoral CD8 cells and any change in percentage of tumoral CD8 cells in response to treatment. Immunohistochemistry will be performed using an anti-CD8 antibody with 3,3' diaminobenzidine chromogen, counterstained with hematoxylin.

The exploratory biomarker objectives of this study are to identify biomarkers associated with nivolumab and microbiome study intervention by assessing tumor tissue and circulating soluble factors, including, but not limited to, DNA, ribonucleic acid (RNA), enzymes, growth factors, cytokines, antibodies, and immune cells in tissue and blood and their association with treatment outcome. Additionally, microbiome profile, DNA, and metabolomics, may be evaluated from stool samples. Changes from baseline in the functional profile of the GI tract will be delineated using metabolomics data sets. Non-parametric and machine learning computational methods will be applied to metabolomic datasets to characterize changes in the functional profile of participants across different study intervention groups. Evaluation of baseline levels and/or changes with study intervention may be performed to determine association with clinical outcomes, including clinical response and resistance, as well as study intervention tolerability.

- Collection of samples for biomarker research is part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the Schedule of Activities (Table 1) and processed in accordance with the laboratory manual:
    - Blood
    - Peripheral blood mononuclear cells (PBMCs)
    - DNA
    - RNA
    - Tumor tissue biopsy, ideally from the same tumor lesion (before and while on study intervention)
    - Stool
- Samples may be tested for genetic analysis on tumor and blood samples, including, but not limited to, assays on circulating free DNA, DNA from tumor, blood, and/or immune cells and T cell receptor sequencing may be performed. This research may evaluate whether genetic variations correspond with outcomes of treatment. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in cancer patients. Circulating soluble analytes may be assessed that may include but are not limited to immune cytokines, growth factors, antibodies, and/or markers associated with immune characteristics and activation or cancer. Additionally, tumor and blood samples will be collected before and on study intervention for immune and/or tumor cell profiling, which may include immune cell phenotyping, enumerations, and/or activation state. Both genome-wide and targeted messenger RNA expression profiling and sequencing in tumor and/or blood may be performed to define gene signatures that correlate with treatment outcomes. Epigenetic analyses may also be performed as these are important biomarkers for some cancers. Stool samples at baseline and on treatment will be evaluated for microbiome and/or metabolite profiling and may be used to determine if there is any association with treatment outcome.
- Other samples may be used for research, including future research to develop methods, assays, prognostics, and/or companion diagnostics related to immuno-oncology

treatment, disease process, pathways associated with disease state, and/or mechanisms of action of checkpoint inhibitor treatment.

8.7.1 Genetics

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be provided in the Laboratory Manual. Samples should be collected for planned analysis of associations between genetic variants in germline/tumor DNA and clinical outcomes to study interventions(s). Blood for planned genetic analysis will be collected for DNA as described in the Schedule of Activities in Section 1.3. If a documented law or regulation prohibits (or local IRB/IEC does not approve) sample collection for these purposes, then such samples should not be collected at the corresponding sites. Additional DNA extracted from planned genetic analysis samples will be stored for future biomedical research only if participant signs the Future Biomedical Research consent.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 7 for Information regarding genetic research.

8.7.2 Enrollment Biomarker

Stool samples are required at screening to assess fecal microbiome composition of the *Ruminococcaceae* abundance-based metric at screening (high, low) for the randomization. This test is required to determine stratification. The test for *Ruminococcaeae* is a laboratory-developed test. It is not an FDA-approved device, and its use is investigational. Sample collection, storage, and shipment instructions are provided in the Laboratory Manual. Quantitative polymerase chain reaction (qPCR) on DNA extracted from stool will be performed and the *Ruminococcaeae* abundance-based metric will be reported.

8.7.3 Exploratory Biomarkers

A fresh tumor biopsy is required at screening (prior to antibiotic or antibiotic placebo administration). An additional on-treatment biopsy is required after 2 infusions with anti-PD-1 study intervention, when medically feasible. An optional biopsy may be obtained during the course of the study or at the time of disease progression, including from participants who respond and subsequently progress. Core needle or incisional tumor biopsy samples are required. Further, every attempt should be made for the on-treatment biopsy(ies) to be taken from the same lesion site. Fine needle aspiration is not allowed.

Blood will be collected for exploratory biomarkers. Blood may be used for whole blood, PBMCs, plasma and/or serum preparation, and nucleic acid extraction. These blood samples will be collected as described in the Schedule of Activities in Section 1.3.

Stool samples will be collected for microbiome analysis, which may include microbiome sequencing and/or metabolites as outlined in the Schedule of Activities in Section 1.3.

Tissue, blood and stool sample collection, storage, and shipment instructions are provided in the Laboratory Manual.

8.7.4 Sample Collection for Long-term Future Biomedical Research

8.7.4.1 Overview of Long-term Future Biomedical Research

Participants in this clinical trial will be asked to consent to provide biological samples for long-term future biomedical research. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of disease and/or their therapeutic treatments. The overarching goal is to use such information to understand disease, safety, and potential treatments for future participants. Such research is for biomarker testing and hypothesis testing to address emergent questions not described elsewhere in the protocol (as part of the main trial).

This research may include genetic and genomic analyses (DNA), gene expression profiling (RNA), proteomics, microbiome, metabolomics (serum, plasma, stool) and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

The collection and submission of biological samples to be stored for long-term future biomedical research must be detailed in the IRB/IEC-approved ICF. Participants who do not wish to participate in the future biomedical research may still participate in the study.

8.7.4.2 Sample Collection

The following samples will be collected and stored in accordance with applicable law for long-term research purposes, including but not limited to, research on biomarkers related to immunotherapies, such as anti-PD-1, and diseases such as cancer or inflammatory disorders:

- Blood, including but not limited to PBMCs, plasma, and/or serum
- DNA
- RNA
- Tumor tissue
- Stool samples

These samples may be sent to one or more laboratories.

For sampling procedures, storage conditions, and shipment instructions, see the Laboratory Manual.

8.7.4.3 Withdrawal from Long-term Sample Storage

Participants have the right to withdraw their consent for the future biomedical research of his/her specimens at any time for any reason and request that their specimens be destroyed. If the participant wishes to withdraw consent for this testing, the Investigator must inform the Sponsor in writing. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received. In the event that the medical records for the main trial are no longer available (eg, if the Investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.7.4.4 Protection of Data Privacy and Data Generation

Participant specimens and associated data will be labeled with a unique participant identification number. Participant medical information associated with the long-term storage of specimens is confidential and may be disclosed to third parties only as permitted by the ICF signed by the participant or as permitted or required by law.

Given the complexity and research nature of the exploratory analyses, data derived from long-term stored specimens will generally not be provided to study Investigators or participants unless required by law.

Data generated from specimens that are stored long term must be available for inspection upon request by representatives of national or local health authorities and Sponsor monitors, representatives, and collaborators as appropriate and as described in Section 10.1.11.

8.8 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESIS

This study is designed to evaluate the safety and tolerability of treatment with 1 of 2 oral microbiome study interventions (FMT or SER-401) in combination with anti-PD-1 therapy in participants with unresectable or metastatic melanoma. The study also intends to assess the

impact on the microbiome profile and assess the association of microbiome study intervention administration with clinical outcomes.

9.2 SAMPLE SIZE DETERMINATION

The study is not intended or powered for hypothesis testing, including comparisons between study intervention groups. The study is intended to provide preliminary estimates of AE rates, response rates, effect sizes and confidence intervals to aid the design of future studies. A sample size of approximately 20 participants per group (FMT, SER-201, and pooled placebo in combination with nivolumab) will provide these preliminary estimates while limiting exposure.

Table 8 provides 95% confidence intervals for the true proportion of responders for a sample size of 20 participants per group. These confidence intervals provide information needed for the design of further studies.

Table 8: Confidence Intervals for the True Proportion of Responders

Observed Proportion of Responders	Lower 95% Confidence Bound	Upper 95% Confidence Bound
0.3	0.119	0.543
0.4	0.191	0.639
0.5	0.272	0.728
0.6	0.361	0.809

9.3 POPULATIONS FOR ANALYSIS

For purposes of analysis, the following populations are defined:

Table 9: Populations for Analysis

Population	Description
Safety Population	All participants who receive at least 1 dose of any study intervention (vancomycin, FMT, SER-401, nivolumab or placebo). Participants will be analyzed according to the study intervention they actually received. Group 2 and Group 3 will be pooled as a single placebo group. Participants enrolled into Group 5 after progression will be included in the Safety Population twice: (1) the pooled placebo group prior to enrollment in Group 5 and (2) Group 5. The Safety Population will be the primary analysis population for all safety analyses.
Antibiotic Safety Population	All participants who receive at least 1 dose of any antibiotic study intervention (vancomycin or placebo).
Microbiome Safety Population	All participants who receive at least 1 dose of any microbiome study intervention (FMT, SER-401 or placebo).
Anti-PD-1 Safety Population	All participants who receive at least 1 dose of nivolumab.

Population	Description
Intent-to-Treat (ITT) Population	All participants randomly assigned to study intervention, regardless of whether any study intervention was administered. Participants will be analyzed according to the study intervention to which they were allocated.
Efficacy Population	All participants randomly assigned to study intervention who receive at least 1 dose of nivolumab and at least 1 dose of any microbiome study intervention (FMT, SER-401 or placebo). Participants will be analyzed according to the study intervention to which they were allocated. Group 2 and Group 3 will be pooled as a single placebo group. Participants enrolled into Group 5 after progression will not be included in the Efficacy Population as Group 5 but will be included as part of the pooled placebo group. The Efficacy Population will be the primary analysis population for all efficacy analyses.
Cross-over Efficacy Population	All participants enrolled in Group 5 who receive at least 1 dose of nivolumab and at least 1 dose of SER-401.

FMT = fecal microbiota transplant; ITT = intent-to-treat; PD-1 = programmed cell death-1

9.4 STATISTICAL ANALYSES

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the study populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. The SAP will serve as a compliment to the protocol and supersedes it in case of differences.

9.4.1 Efficacy Analyses

The analyses for clinical activity will be performed on the Efficacy Population, consisting of all participants randomly assigned to study intervention who receive at least 1 dose of nivolumab and at least 1 dose of any microbiome study intervention (FMT, SER-401, or placebo). Participants will be analyzed according to the study intervention to which they were allocated. Participants randomly allocated to either of the placebo groups (Group 2 or Group 3) will be pooled as a single placebo group for all efficacy analyses. A subset of efficacy analyses will also be conducted on the intent-to-treat (ITT) Population, as described in the SAP.

Analyses of efficacy endpoints (secondary and exploratory) will be adjusted for the fecal microbiome composition of the *Ruminococcaceae* abundance-based metric at screening (high, low).

This study is not intended or powered for hypothesis testing, including comparisons between study intervention groups. Due to the exploratory nature of this study, no control of type I error will be applied for any of the endpoints.

9.4.1.1 Primary Efficacy Endpoints

There are no primary efficacy objectives or endpoints for this study.

9.4.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include:

- ORR: Defined as CR or PR as best response by RECIST v1.1 assessment. Participants who do not have RECIST assessment for any reason will be counted as not responding.
- DCR: Defined as CR, PR, or stable disease (SD) for ≥ 24 weeks as best response by RECIST v1.1. Participants who do not have RECIST assessment for any reason will be counted as not responding.
- PFS: Defined as the time from randomization to date of first documented radiographic progression of disease or date of death due to any cause, whichever occurs first. Participants who have not progressed or died will be censored at the last tumor assessment date.
- PFS rate at 1 year: Defined as the proportion of participants without documented progression of disease or death due to any cause at 1 year.
- OS: Defined as the time from randomization until death due to any cause. Participants who have not died will be censored at the most recent contact date they were known to be alive.
- OS rate at 1 year: Defined as the proportion of participants alive at 1 year.
- Duration of response: Defined as time from date of documented CR or PR to date of first documented radiographic progression of disease or date of death due to any cause, whichever occurs first. Participants who have not progressed or died will be censored at the last tumor assessment date.

Response rates for ORR, DCR, PFS, and OS will be estimated within each study intervention group and 95% confidence intervals (CIs) will be estimated using the Clopper-Pearson method. PFS and OS will be estimated using Kaplan-Meier techniques, and the median survival time and 95% CIs will be estimated within each study intervention group.

9.4.1.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include:

- ORR in participants who receive SER-401 after progressing while on placebo (Group 5).
- DCR in participants who receive SER-401 after progressing while on placebo (Group 5).
- PFS rate at 1 year in participants who receive SER-401 after progressing while on placebo (Group 5).
- OS rate at 1 year in participants who receive SER-401 after progressing while on placebo (Group 5).

The above exploratory endpoints will be analyzed on the Cross-over Efficacy Population. Further analysis details will be described in the SAP.

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Population, consisting of all participants who receive at least 1 dose of any study intervention (vancomycin, FMT, SER-401, nivolumab, or placebo). Participants will be analyzed according to the study intervention they actually received. A subset of safety analyses will also be conducted on the Anti-PD-1 Safety Population, as described in the SAP.

Safety will be assessed through summaries of AEs, laboratory test results (hematology and serum chemistry), vital signs, ECGs, and ECOG performance score. Verbatim descriptions of treatment-emergent AEs (defined in Section 10.5.1.4) will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA), and their incidence will be summarized by study intervention group. In addition, separate summaries will be generated for AESIs, SAEs, deaths, AEs leading to study discontinuation, and AEs leading to treatment discontinuation.

Safety analyses will also be performed for events and assessments that occur during the antibiotic/microbiome lead-in phase. Events and assessments occurring during the antibiotic or antibiotic placebo administration and washout (Day -14 to Day -7) will be summarized for the Antibiotic Safety Population, defined as all participants who receive at least 1 dose of any antibiotic study intervention (vancomycin or placebo). Events and assessments occurring during the microbiome lead-in (Day -7 to Cycle 1 Day 1) will be summarized for the Microbiome Safety Population, defined as all participants who receive at least 1 dose of any microbiome study intervention (FMT, SER-401 or placebo).

9.4.3 Other Analyses

The number of participants who were screened, enrolled and treated, enrolled and not treated, and completed the study will be presented in summary tables. The reason for discontinuation from the study will be listed by participant and summarized in a table. The number of participants in each study intervention group and analysis population will be summarized.

Demographic and baseline characteristics of the study population will be summarized overall and for each study intervention group. Categorical measures will be summarized using frequencies and percentages. Continuous variables will be summarized using means, standard deviations, medians, minimums, and maximums.

9.4.3.1 Biomarker Analyses

The secondary biomarker endpoints include:

- Determination of the engraftment of FMT or SER-401 bacteria into each of the microbiome study intervention groups relative to placebo.
- Change in the percentage of CD8 cells in tumor tissue from baseline at Cycle 2.

The exploratory biomarker endpoints include:

- Changes in the composition of the fecal microbiome from baseline to on treatment following administration of FMT, SER-401, or placebo.
- Functional changes in transcriptomic, metabolomic, and/or proteomic profiles from baseline to on treatment.
- Association of T-cell phenotypic characteristics and immune characteristics in the tumor with clinical outcomes (eg, ORR, DCR, PFS, OS) and/or AEs.
- Molecular (genomic, metabolic, and/or proteomic) or microbial biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or mechanism of action of anti-PD-1 therapy and their relationship to microbiome study intervention administration.

Absolute change in percentage of CD8 tumoral cells will be summarized by study intervention group using means and 95% CIs. Other biomarker analyses will be performed as described in Section 8.7.

9.5 INTERIM ANALYSES

No interim analyses are planned for this study.

9.5.1 Data Monitoring Committee

Ongoing safety data review will be conducted by the Data Monitoring Committee (DMC). This is a committee that is formed of select Sponsor personnel, including the Medical Monitor and representatives from other functions including, but not limited to, Biostatistics, Clinical Science, and Drug Safety. Members of the DMC will be unblinded to participant treatment assignment. To ensure participants' safety during the study, the DMC will review the emerging safety data on a regular basis. Roles and responsibilities of the DMC will be detailed in a separate charter.

Safety monitoring will include unblinded evaluation of all AEs, AESIs, SAEs, relevant protocol deviations, and laboratory data. If the DMC deems a benefit-risk assessment necessary, the DMC may also review unblinded efficacy data. The DMC may decide to stop the study early or suspend enrollment of a study intervention group for safety reasons.

Study-holding criteria as described in Section 7.1.1 will be adjudicated by the DMC per the study-specific DMC charter.

For safety monitoring purposes, a trial-limiting toxicity is defined as:

1. Any event listed in Table 4.
2. Any SAE assessed as at least possibly related to the study intervention.
3. Any AESI (defined in Section 8.3.7) assessed as at least possibly related to the microbiome study interventions.

A Bayesian rule will be employed to monitor toxicity throughout the study (Table 10). A minimally informative beta (0.5, 2.5) prior has been assumed. For each study intervention group, if the number of participants with a trial-limiting toxicity (defined above) is greater than or equal to the number in Table 10, then enrollment and dosing of that study intervention group will be immediately halted, as it is likely that the toxicity rate is >30%, as noted by the Bayesian posterior probabilities. The rule is intentionally conservative early in the enrollment phase. If administration of a study intervention group is halted, all available safety data will be reviewed by an independent medical monitor who will determine, in consultation with the DMC, whether to resume administration of study intervention and/or enrollment.

Table 10: Stopping Rules for Trial-limiting Toxicity Rate Greater Than 30%

Participants administered study intervention within a group	10	15	20
Participants with Trial-limiting Toxicity	4	6	9
Posterior Probability [toxicity rate >30%]	0.61	0.69	0.87

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Compliance with Laws and Regulations

This study will be conducted in full conformance with the International Council for Harmonisation (ICH) E6 guideline for Good Clinical Practice and the consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, and applicable laws and regulations. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

10.1.2 Institutional Review Board or Independent Ethics Committee

The protocol, protocol amendments, ICF(s), Investigator's Brochure, any information to be given to the participant, and relevant supporting information must be submitted to the IRB/IEC and reviewed and approved by the IRB/IEC before the study is initiated. In addition, any participant recruitment materials (eg, advertisements) must be approved by the IRB/IEC.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants or changes that involve logistical or administrative aspects only (eg, change in Medical Monitor or contact information).

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Promptly documenting and reporting any deviations that might have an impact on participant safety and data integrity to the Sponsor and to the IRB/IEC in accordance with established requirements, policies and procedures

- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.3 Financial Disclosure

Investigators and Sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 4.5).

10.1.4 Informed Consent

The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

The ICF will contain separate signature sections for the following procedures which include: 1) blood, tumor, and stool samples for biomarker analysis intended to be used for **future or exploratory** research purposes and 2) a tumor biopsy at the time of disease progression or additional on-treatment timepoint.

The Investigator or authorized designee will explain to each participant the objectives, methods, and potential risks associated with each optional procedure. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a participant's agreement to participate in optional procedures. Participants who decline to participate will not provide a separate signature.

Participants must be re-consented to the most current version of the ICF(s) (or to a significant new information/findings addendum in accordance with applicable laws and IRB/IEC policy) during their participation in the study. The medical record should document the re-consent process and that written informed consent was obtained using the updated/revised ICF for continued participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative. All signed and dated ICFs must remain in the participant's study file or in the site study file and must be available for verification by study monitors at any time.

The final revised IRB/IEC-approved ICFs must be provided to the Sponsor for the purpose of health authority submission.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

A participant who receives placebo in Groups 2 or 3 and has radiographic evidence of progression of disease while on study and agrees to receive active SER-401 and nivolumab treatment as part of a cross-over to Group 5 will be required to sign another ICF prior to entering Group 5.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.5 Data Protection

The Sponsor maintains confidentiality standards by assigning a unique participant identification number to each participant enrolled in the study. This means that participant names are not included in data sets that are transmitted to any Sponsor location.

Participant medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the participant or as permitted or required by law.

Medical information may be given to a participant's personal physician or other appropriate medical personnel responsible for the participant's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives and collaborators, and the IRB/IEC for each study site, as appropriate.

10.1.6 Dissemination of Clinical Study Data

The results of this study may be reported to the public, in the form of a publication or presentation at scientific congresses, before completion of the study.

10.1.7 Administrative Structure

This trial will be sponsored and managed by the Parker Institute for Cancer Immunotherapy. The Sponsor will provide clinical operations management, data management, medical monitoring, and safety oversight.

Central facilities will be used for certain study assessments throughout the study (eg, specified laboratory tests and biomarker analyses), as specified in Section 8.2.5 and Section 8.7, respectively. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

10.1.8 Data Quality Assurance

All participant data relating to the study will be collected via the electronic data collection (EDC) system on an eCRF unless transmitted to the Sponsor or designee electronically (eg, central laboratory data, biomarker and other biological sample data). Sites will be responsible for data entry into the EDC system and will receive training for appropriate eCRF completion. The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing and dating the eCRF.

The Investigator must maintain accurate documentation (source data, see Section 10.1.9) that supports the information entered in the eCRF. The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor is responsible for the data management of this study, including quality checking of the data. Study monitors will perform ongoing source data verification to confirm that data entered on the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH Good Clinical Practice (GCP), and all applicable regulatory requirements.

At the end of the study, the Investigator will receive participant data for his/her site in a readable format on a compact disc (or other readable digital format) that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

10.1.9 Source Documentation

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site. Data entered on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request

previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Source documents (paper or electronic) are those in which participant data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, clinical outcome assessment (COA)/patient reported outcomes (PRO), evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

When clinical observations are entered directly into a study site's computerized medical record system (ie, in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

Source documents that are required to verify the validity and completeness of data entered on the eCRFs must not be obliterated or destroyed and must be retained as described in Section 10.1.12.

10.1.10 Study and Site Closure

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Reasons for terminating the study may include, but are not limited to, the following:

- Discontinuation of further study intervention development
- The incidence or severity of AEs in this or other studies indicates the potential hazard to participants
- Participant enrollment is unsatisfactory

The Sponsor will notify the Investigator if the Sponsor decides to discontinue the study.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Poor protocol adherence
- Inaccurate or incomplete data recording

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- No study activity (ie, all participants have completed the study and all obligations have been fulfilled)

10.1.11 Site Inspections

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, participants' medical records, and eCRFs. The Investigator will permit national and local health authorities; Sponsor monitors, representatives and collaborators; and the IRBs/IECs to inspect facilities and records relevant to this study.

10.1.12 Retention of Records

Records and documents pertaining to the conduct of this study and distribution of the investigational medicinal product, including signed eCRFs, electronic or paper COA/PROs data (if applicable), signed informed consent forms, laboratory test results, and medication inventory records, must be retained by the Investigator for the maximum period required by applicable regulations of relevant national or local health authorities. No records may be disposed of without the written approval of the Sponsor. The Sponsor will notify the Investigator when the records are no longer needed. Following notification from the Sponsor, the documents may be destroyed, subject to local regulations.

Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

10.1.13 Publication Policy and Protection of Trade Secrets

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results.

The Investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a Coordinating Investigator will be designated in accordance with the Parker Institute for Cancer

Immunotherapy publication policy. Authorship will be based on overall scientific contribution and participant enrollment.

10.2 APPENDIX 2: EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP: Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

10.3 APPENDIX 3: RECIST CRITERIA (VERSION 1.1)

Tumor response will be assessed according to RECIST v1.1 (Eisenhauer et al., 2009) as described below.

10.3.1 Measurability of Tumor at Baseline

At baseline, tumor lesions/lymph nodes will be categorized as measurable or nonmeasurable as follows:

- **Measurable**

  Tumor lesions: Must be accurately measured in ≥ 1 dimension (longest diameter in the plane of measurement to be recorded) with a minimum size of:

  - 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
  - 10 mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable)
  - 20 mm by chest X-ray

  Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

- **Nonmeasurable**

  - All other lesions (or disease sites), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis)
  - Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques

10.3.2 Tumor Response Evaluation

10.3.2.1 Baseline Documentation of Target and Nontarget Lesions

- **Target lesions**
  - When > 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions
  - It may be the case that, on occasion, the largest lesion which can be measured reproducibly should be selected
- **Nontarget lesions**
  - All other lesions (or disease sites), including pathological lymph nodes, should be identified as nontarget lesions
  - It is possible to record multiple nontarget lesions involving the same organ as a single item (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases')

10.3.2.2 Evaluation of Target Lesions

Target lesions will be evaluated and response recorded as defined in Appendix Table 1.

Appendix Table 1: Response Based on Evaluation of Target Lesions at Each Assessment

Complete response	Disappearance of all target lesions; if a pathologic lymph node, reduction in the shortest axis to < 10 mm[a]
Partial response[b]	≥ 30% decrease in the sum of the diameters of target lesions relative to the baseline sum diameters[c]
Stable disease[b,d]	Neither a sufficient reduction to qualify as a partial response nor a sufficient increase to qualify as progression[c]
Progressive disease[b]	≥ 20% increase in the sum diameters relative to the smallest sum diameters recorded (including the baseline sum diameters) in conjunction with an increase of at least 5 mm in that smallest sum diameters, or the appearance of 1 or more new lesions[c,e]

[a] For each pathologic lymph node considered a target lesion, the node must have a short axis measuring < 10 mm to be considered as a complete response. In such cases, the sum diameters may not be zero (as a normal lymph node can have a short axis of < 10 mm).

[b] For each pathologic lymph node considered a target lesion, the measurement of the short axis of the node is to be included in the sum diameters when determining partial response, stable disease, and progression.

[c] In this study, the "baseline sum diameters" is calculated based on the lesion measurements obtained at screening.

[d] Duration of stable disease is measured from the date of the first dose of study intervention until criteria for progressive disease are met based on the smallest sum diameters recorded (including the baseline sum diameters).

[e] The finding of a new lesion should be unequivocal and not possibly attributable to a difference in imaging modality or scanning technique. Post-baseline, fluorodeoxyglucose positron emission tomography (FDG-PET) may be useful in assessing new lesions apparent on CT scan.

10.3.2.3 Evaluation of Nontarget Lesions

Nontarget lesions will be evaluated and response recorded as defined in Appendix Table 2.

Appendix Table 2: Response Based on Evaluation of Nontarget Lesions at Each Assessment

Complete response	Disappearance of all non-target lesions; all lymph nodes must be nonpathologic in size (ie, < 10 mm on the short axis)
Not complete response nor progressive disease	Persistence of 1 or more non-target lesions
Progressive disease	Unequivocal progression[a] of any existing non-target lesion or the appearance of 1 or more new lesions[b]

[a] The participant should stop study intervention, even in the presence of a partial response or stable disease, based on assessment of target lesions.

[b] The finding of a new lesion should be unequivocal and not possibly attributable to a difference in imaging modality or scanning technique. Post-baseline, fluorodeoxyglucose positron emission tomography (FDG-PET) may be useful in assessing new lesions apparent on computerized tomography (CT) scan.

10.3.2.4 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (eg, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the participant's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan as report as a 'new' cystic lesion, which it is not.

10.3.2.5 Evaluation of Overall Response

Overall response based on the evaluation of target and nontarget lesions will be determined as shown in Appendix Table 3.

Appendix Table 3: Evaluation of Overall Response at Each Assessment

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
Complete response	Complete response	No	Complete response
No target lesion[a]	Complete response	No	Complete response
Complete response	Not evaluable[b]	No	Partial response
Complete response	Not complete response/ non-progressive disease	No	Partial response

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
Partial response	Non-progressive disease and not evaluable[b]	No	Partial response
Stable disease	Non-progressive disease and not evaluable[b]	No	Stable disease
Not all evaluated	Non-progressive disease	No	Not evaluable
No target lesion[a]	Not all evaluated	No	Not evaluable
No target lesion[a]	Non-complete response/ non-progressive disease	No	Non-complete response/ non-progressive disease
Progressive disease	Any	Yes or no	Progressive disease
Any	Progressive disease	Yes or no	Progressive disease
Any	Any	Yes	Progressive disease
No target lesion[a]	Unequivocal progressive disease	Yes or No	Progressive disease
No target lesion[a]	Any	Yes	Progressive disease

[a] Defined as no target lesions at baseline.

[b] Not evaluable is defined as either when no or only a subset of lesion measurements are made at an assessment.

10.4 APPENDIX 4: CLINICAL LABORATORY TESTS

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol and the protocol appendix for each respective combination.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

10.5 APPENDIX 5: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.5.1 Definitions

10.5.1.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events Meeting the AE Definition
• Any abnormality or deterioration in a laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the Investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • A new condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. • Serious events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study procedures (eg, screening invasive procedures, such as biopsies, discontinuation of study intervention). • Any new cancer (that is not a condition of the study) including basal and squamous cell carcinoma. • Note: Progression of the cancer under study is not a reportable event. Refer to Section 8.3.6 for additional details.

Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

10.5.1.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any AE that suggests a significant hazard, contraindication, side effect, or untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. Note: Hospitalizations for the following reasons are not considered SAEs in this study: • a visit to the emergency room or other hospital department for < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)

- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

In offspring of a participant exposed to the study intervention regardless of timing as determined for study intervention based on product half-life. Any spontaneous abortion should be reported in the same fashion (as the Sponsor considers spontaneous abortions to be medically significant).

f. Other important medical events:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.5.1.3 Definition of Unexpected AE

Unexpected AE Definition

- Any AE, the specificity or severity of which is not consistent with the current Investigator's Brochure. Expected means that the event has previously been observed with the study intervention and is identified and/or described in the current IB. It does not mean that the event is expected with the underlying disease(s), co-morbidities or concomitant medications.

10.5.1.4 Definition of Treatment-emergent AE

Treatment-emergent AE Definition
• Any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding that is considered to be clinically significant), syndrome or disease that either occurs during the study, having been absent at baseline, or, if present at baseline, appears to have worsened in severity or frequency, whether or not the event is considered related to the study intervention.

10.5.2 Additional Events Reported in the Same Manner as an SAE

Additional Events Reported in the Same Manner as a SAE
• In addition to the SAE criteria in Section 10.5.1.2, AEs meeting any of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes. o A new invasive or malignant cancer (not the indicated condition of the study) o An overdose or is an associated event that meets safety criterion with an overdose (as specified in Section 8.4) o Protocol-specified AESIs (as defined in Section 8.3.7) o Pregnancy (as specified in Section 8.3.5)

10.5.3 Recording AEs and SAEs

AE and SAE Recording
• When an AE/AESI/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. Only a single AE term should be recorded for the event. • The Investigator will record all relevant AE/AESI/SAE information in the eCRF. • It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Adverse Event eCRF/SAE report form. • There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/AESI/SAE.

Assessment of Severity

- The terms 'severe' and 'serious' are not synonymous. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe. Severity (intensity) and seriousness need to be independently assessed for each AE recorded on the eCRF.
- The Investigator will assess the intensity for each AE, including AESI, and SAE (and other reportable safety events) according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0, which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
  The following grading will be used for assessing intensity for AEs not specifically listed in the NCI CTCAE:
    - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
    - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
    - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
    - Grade 4: Life threatening consequences; urgent intervention indicated.
    - Grade 5: Death related to AE.
- Any changes to CTCAE grade over the course of a given episode (ie, persistent AE) will have each change of grade recorded on the Adverse Event CRFs.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/AESI/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use their clinical judgment, knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine the relationship.
- The following guidance will be considered and investigated:
    - Temporal relationship of the event onset to study intervention administration

- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study intervention, or reintroduction of study intervention (as applicable)
- Known association of the event with the study intervention or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the participant or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/AESI/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/AESI/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- For studies in which multiple agents are administered as part of a combination regimen, the Investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the Investigator's opinion, there are sufficient data to support full attribution of the AE to the single agent.

Causality of AEs, AESIs, and SAEs in this protocol will be assessed as follows:

- **Unrelated**: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).

  Note: If an AE is assessed as unrelated to the study intervention(s), there must be an alternative etiology in the Investigator's assessment for that event documented in the participant's medical records.
- **Unlikely Related**: This category applies to those AEs that are judged to be unrelated to the study intervention(s), but for which no extraneous cause may be found. An AE may be considered unlikely to be related to study intervention(s) if or when it meets 2 of the following criteria:

- it does not follow a reasonable temporal sequence from administration of the study intervention(s);
- it could readily have been produced by the participant's clinical state, environmental or toxic factors, or other modes of therapy administered to the participant;
- it does not follow a known pattern of response to the study intervention(s); or
- it does not reappear or worsen when the study intervention(s) is re-administered.

- **Possibly Related**: This category applies to those AEs for which a connection with the study intervention administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria:
  - it follows a reasonable temporal sequence from administration of the study intervention(s);
  - it could not readily have been produced by the participant's clinical state, environmental or toxic factors, or other modes of therapy administered to the participant; or
  - it follows a known pattern of response to the study intervention(s).
- **Probably Related**: This category applies to those AEs that the Investigator feels with a high degree of certainty are related to the study intervention(s). An AE may be considered probably related if or when it meets 3 of the following criteria:
  - it follows a reasonable temporal sequence from administration of the study intervention(s);
  - it could not be reasonably explained by the known characteristics of the participant's clinical state, environmental or toxic factors, or other modes of therapy administered to the participant;
  - it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the study intervention, yet study intervention relatedness clearly exists; for example, as in bone marrow depression, fixed study intervention eruptions, or tardive dyskinesia); or
  - it follows a known pattern of response to the study intervention(s).
- **Definitely Related**: This category applies to those AEs that the Investigator believes are incontrovertibly related to study intervention(s). An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria:
  - it follows a reasonable temporal sequence from administration of the study intervention(s);
  - it could not be reasonably explained by the known characteristics of the participant's clinical state, environmental or toxic factors, or other modes of therapy administered to the participant;

- it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to study intervention(s) (if rechallenge occurs); and
- it follows a known pattern of response to the study intervention(s).

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded on the eCRF.
- The Investigator will submit any updated data related to SAEs or AESIs to the Sponsor within 24 hours of receipt of the information.

10.5.4 Reporting of AEs, AESIs, SAEs, and Other Reportable Safety Events to the Sponsor

Reporting of AEs, AESIs, SAEs, and Other Reportable Safety Events to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting AEs to the Sponsor will be via the electronic data collection (EDC) tool.
- Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE reporting tool (see next section).
- Reference Section 8.3.1– Time Period and Frequency for Collecting AE, AESI, SAE, and Other Reportable Safety Event Information for reporting time requirements
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- The site will report all AESIs on the study-specific SAE report form to the Parker Institute for Cancer Immunotherapy study team within 24 hours of site awareness. The AESI should also be reported on the Adverse Event eCRF.
- The site will report all SAE data on the study-specific SAE report form to the Parker Institute for Cancer Immunotherapy study team within 24 hours of site awareness.

- Contacts for reporting SAEs, AESIs, and other reportable safety event can be found in Section 8.3.8.2.

SAE and Other Reportable Safety Event Reporting to the Sponsor

- In the instance where an SAE or AESI occurs, a facsimile transmission of the SAE report form and/or Pregnancy form is the preferred method to transmit this information to the Parker Institute for Cancer Immunotherapy Pharmacovigilance Group.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE report form sent via email.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE report form within the designated reporting time frames.
- Contacts for SAE, AESI, and other reportable safety event reporting can be found in Section 8.3.8.2.

10.5.5 Additional Reporting Considerations

AE and SAE Recording for Special Circumstances

Diagnosis versus Signs and Symptoms

- Symptoms reported on the diary cards should be assessed by the Investigator for clinical significance and should be added as an Adverse Event according to the Investigator's judgement or CTCAE 5.0 criteria, if appropriate.
- A diagnosis (if known) or cause of death should be recorded on the Adverse Event eCRF page rather than individual signs and symptoms (eg, record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases).
- If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded separately on the Adverse Event eCRF page.
- If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

Adverse Events That Are Secondary to Other Events

- In general, AEs that are secondary to other events (eg, cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the

initiating event should be recorded as an independent event on the Adverse Event eCRF page. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all 3 events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

- All AEs should be recorded separately on the Adverse Event eCRF page if it is unclear as to whether the events are associated.

Persistent or Recurrent Adverse Events

- A persistent AE is one that extends continuously, without resolution, between participant evaluation time points. Such events should only be recorded once on the Adverse Event eCRF page. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported.
- If a persistent AE becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF page, and details regarding any increases or decreases in severity will be captured on the Adverse Event eCRF.
- If the event becomes serious, it should be reported to the Sponsor as an SAE, and the Adverse Event eCRF page should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to SAEs.
- A recurrent AE is one that resolves between participant evaluation time points and subsequently recurs. Each recurrence of an AE should be recorded as a separate event on the Adverse Event eCRF page.

Abnormal Laboratory Values

- A clinical laboratory test value must be reported as an AE if it meets any of the following criteria:
  - is accompanied by clinical symptoms
  - results in a change in study intervention (eg, dose modification, treatment interruption, or treatment discontinuation)
  - results in a medical intervention or change in concomitant medication
  - is clinically significant in the Investigator’s judgment

Abnormal Vital Sign Values

- Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.
- If a clinically significant vital sign abnormality is a sign of a disease or syndrome (eg, high blood pressure), only the diagnosis (ie, hypertension) should be recorded on the Adverse Event eCRF page.
- Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF page (see above for details on recording persistent AE).

Abnormal Liver Function Tests

- The finding of an elevated ALT or AST (> 3 x baseline value) in combination with either an elevated total bilirubin (>2 x ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, Investigators must report as an AE the occurrence of either of the following:
    - Treatment-emergent ALT or AST > 3 x baseline value in combination with total bilirubin > 2 x ULN (of which ≥ 35% is direct bilirubin)
    - Treatment-emergent ALT or AST > 3 x baseline value in combination with clinical jaundice
- The most appropriate diagnosis or if a diagnosis cannot be established, the abnormal laboratory values should be recorded on the Adverse Event eCRF page and reported to the Sponsor immediately as an SAE or an AESI (see Section 8.3.7).

Lack of Efficacy or Worsening of Underlying Disease

- Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

Deaths

- All deaths that occur during the protocol-specified AE reporting period, regardless of relationship to study intervention, must be recorded on the Death eCRF page and immediately reported to the Sponsor (see Section 8.3.1), unless the death is attributed to progression of disease.
- Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical

concept on the Adverse Event eCRF page. Generally, only one such event should be reported.

- If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF page and reported as an SAE.
- If the cause of death later becomes available (eg, after autopsy), "unexplained death" should be replaced by the established cause of death.
- The term "sudden death" should not be used unless combined with the presumed cause of death (eg, "sudden cardiac death").
- If the death is attributed to progression of underlying disease, “underlying disease" should be recorded on the appropriate eCRF page; no SAE form is necessary.
- Deaths that occur after the AE reporting period should be reported as described in Section 8.3.2.

Pre-existing Medical Conditions

- A pre-existing medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the Medical History eCRF page.
- A pre-existing medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF page, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (eg, "more frequent headaches").

Adverse Events Associated with Overdose or Error in Drug Administration

- An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study intervention is not itself an AE, but it may result in an AE. All AEs associated with an overdose or incorrect administration of study intervention should be recorded on the Adverse Event eCRF page.
- If the associated AE fulfills seriousness criteria, the event should be reported to the Sponsor as a separate-SAE.

10.6 APPENDIX 6: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

10.6.1 Definitions

10.6.1.1 Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories **are not considered WOCBP**

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

    Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
    - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone level > 40 mIU/mL to confirm menopause.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.6.2 Contraception Guidance:

10.6.2.1 Male Participants

Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame and at least 7 months after the last dose of study intervention.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure, defined as at least 7 months after the end of study intervention.

- Female partners of males participating in the study to consider use of effective methods of contraception as described in Appendix Table 4 until the end of relevant systemic exposure, defined as at least 7 months after the end of study intervention in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame and at least 7 months after the last dose of study intervention.
- Refrain from donating sperm for the duration of the study and at least 7 months after the last dose of study intervention.

10.6.2.2 Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Appendix Table 4 during study duration and until the end of relevant systemic exposure, defined as at least 5 months after the end of study treatment.

Appendix Table 4: Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[a]
• Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS)

• Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in the SOA (Section 1.3). • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence.
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 5 months after the last dose of study intervention

10.6.3 Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test within 24 hours of first dose of study intervention.
- Additional pregnancy testing should be performed at every 4 weeks prior to nivolumab administration during the treatment period, at the End of Treatment visit (ie, 30 days after the last dose of study intervention), at the Follow-up visit 100 days after the last dose of study interventions, and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

10.6.4 Collection of Pregnancy Information

10.6.4.1 Male Participants with Partners who Become Pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.6.4.2 Female Participants who Become Pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.7 APPENDIX 7: GENETICS

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact immune response, drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood and tumor sample will be collected for DNA analysis from consenting participants.
- Stool samples will be collected, and microbiome DNA extracted and analyzed to evaluate a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to bacterial genetic determinants that impact immune response, drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug.
- Germline, tumor and bacterial DNA samples will be used for research related to anti-PD-1 therapy or cancer and/or immune disorders and related diseases or evaluation of new assay technologies. They may also be used to develop tests/assays including diagnostic tests related to treatment, including anti-PD-1 therapy, and cancer. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- DNA samples may be analyzed for whole genome sequencing and bacterial DNA may be analyzed by 16s and/or whole metagenomic sequencing and relationship to clinical outcomes in response to study intervention. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to anti-PD-1 therapy or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on anti-PD-1 therapy or study intervention continues in accordance with applicable law.

10.8 APPENDIX 8: PARTICIPANT DIARY

Site Number: _____ Participant Study Number: _____

PICI0014 Participant Diary

Study Period: **Antibiotic (Vancomycin) Lead-In**

Bring this diary to your next clinic visit.

Daily Dosing: Each day take your antibiotic or antibiotic placebo 4 times and record the following below:

- Write the time you took your capsule
- Circle am or pm
- If you miss a dose, circle missed this dose.

	Day 1 Date:	Day 2 Date:	Day 3 Date:	Day 4 Date:
Dose 1	Time_____ am / pm missed this dose	Time_____ am / pm missed this dose	Time_____ am / pm missed this dose	Time_____ am / pm missed this dose
Dose 2	Time_____ am / pm missed this dose	Time_____ am / pm missed this dose	Time_____ am / pm missed this dose	Time_____ am / pm missed this dose
Dose 3	Time_____ am / pm missed this dose	Time_____ am / pm missed this dose	Time_____ am / pm missed this dose	Time_____ am / pm missed this dose
Dose 4	Time_____ am / pm missed this dose	Time_____ am / pm missed this dose	Time_____ am / pm missed this dose	Time_____ am / pm missed this dose

If you have any questions or concerns
Contact Study Team/Research Nurse/Study Doctor at_____
Completed by: Participant Signature _____ Date_____
Reviewed by: Study Personnel Signature _____ Date_____

Site Number: _____ Participant Study Number: _____

PICI0014 Participant Diary

Study Period: **SER-401/Placebo Microbiome Lead-In**

Bring this diary to your next clinic visit.

Daily Dosing:

- Your study capsules should be taken at approximately the same time each morning following an overnight fast (no food or drink except for small amounts of water).
- Take study capsules with 8 ounces of water (capsules are to be swallowed, not chewed).
- Complete the information below for each day

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date							

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Did you take your capsules today?	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No
What time?	_____ am / pm	_____ am / pm	_____ am / pm	_____ am / pm	_____ am / pm	_____ am / pm	_____ am / pm

Temperature:

- Take your oral temperature each day at approximately the same time and record.
- Ensure no recent (within 30 minutes) drinking of hot or cold beverage or smoking.
- If you did not take your temperature, circle (Did not take my temperature today)

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
What was your temperature today?	°F	°F	°F	°F	°F	°F	°F
	or	*or*	*or*	*or*	*or*	*or*	*or*
	Did not take my temperature today	Did not take my temperature today	Did not take my temperature today	Did not take my temperature today	Did not take my temperature today	Did not take my temperature today	Did not take my temperature today

If you have any questions or concerns

Contact Study Team/Research Nurse/Study Doctor at_____

Completed by: Participant Signature _____ Date_____

Reviewed by: Study Personnel Signature _____ Date_____

Site Number: _____ Participant Study Number: _____

PICI0014 Participant Diary

Study Period: **SER-401/Placebo Microbiome Lead-In (page 2)**

Bring this diary to your next clinic visit.

Side Effects: Each Day (circle) the most severe intensity for each symptom that you experienced on a day:
0 = no symptom
1 = mild: I noticed the symptom. It did not keep me from going about my normal activities.
2 = moderate: I noticed the symptom and it kept me from doing some of my normal activities.
3 = severe: I noticed the symptom and it kept me from doing activities that I really needed and wanted to do.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Gas or flatulence	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3
	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Abdominal discomfort (distention, bloating, pain or cramping)	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3
Vomiting	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3
Constipation	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3

Diarrhea: If you have diarrhea any day, (circle) the severity in the table below:
None
Mild = 3-4 unformed bowel movements per day
Moderate = 5-6 unformed bowel movements per day
Severe = 7 or more unformed bowel movements per day
Call your study doctor if you experience severe diarrhea for more than 2 days in a row

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Diarrhea	None	None	None	None	None	None	None
	Mild	Mild	Mild	Mild	Mild	Mild	Mild
	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
	Severe	Severe	Severe	Severe	Severe	Severe	Severe

If you have any questions or concerns
Contact Study Team/Research Nurse/Study Doctor at_____
Completed by: Participant Signature _____ Date_____
Reviewed by: Study Personnel Signature _____ Date_____

Site Number: _____ Participant Study Number: _____

PICI0014 Participant Diary

Study Period: **FMT/Placebo Microbiome Lead-In**

Bring this diary to your next clinic visit.

You will come to the study site 3 times over 7 days to receive your FMT/Placebo.

Temperature:

- Take your oral temperature each day at approximately the same time and record.
- Ensure no recent (within 30 minutes) drinking of hot or cold beverage or smoking.
- If you did not take your temperature, circle Did not take my temperature today.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
What was your temperature today?	°F	°F	°F	°F	°F	°F	°F
	or	*or*	*or*	*or*	*or*	*or*	*or*
	Did not take my temperature today	Did not take my temperature today	Did not take my temperature today	Did not take my temperature today	Did not take my temperature today	Did not take my temperature today	Did not take my temperature today

Side Effects: Each Day circle the most severe intensity for each symptom that you experienced on a day:
0 = **no symptom**
1 = **mild**: I noticed the symptom. It did not keep me from going about my normal activities.
2 = **moderate**: I noticed the symptom and it kept me from doing some of my normal activities.
3 = **severe**: I noticed the symptom and it kept me from doing activities that I really needed and wanted to do.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Gas or flatulence	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3
Abdominal discomfort (distention, bloating, pain or cramping)	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3
Vomiting	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3
Constipation	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3

If you have any questions or concerns
Contact Study Team/Research Nurse/Study Doctor at_____
Completed by: Participant Signature _____ Date_____
Reviewed by: Study Personnel Signature _____ Date_____

Site Number: _____ Participant Study Number: _____

PICI0014 Participant Diary

Study Period: **FMT/Placebo Microbiome Lead-In (page 2)**

Bring this diary to your next clinic visit.

Diarrhea: If you have diarrhea any day, (circle) the severity in the table below:
None
Mild = 3-4 unformed bowel movements per day
Moderate = 5-6 unformed bowel movements per day
Severe = 7 or more unformed bowel movements per day
Call your study doctor if you experience severe diarrhea for more than 2 days in a row

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Diarrhea	None	None	None	None	None	None	None
	Mild	Mild	Mild	Mild	Mild	Mild	Mild
	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
	Severe	Severe	Severe	Severe	Severe	Severe	Severe

If you have any questions or concerns
Contact Study Team/Research Nurse/Study Doctor at_____
Completed by: Participant Signature _____ Date_____
Reviewed by: Study Personnel Signature _____ Date_____

Site Number: _____ Participant Study Number: _____

PICI0014 Participant Diary

Study Period: **SER-401/Placebo with Nivolumab Cycle __ Week __**

Bring this diary to your next clinic visit.

Daily Dosing:

- Your study capsules should be taken at approximately the same time each morning following an overnight fast (no food or drink except for small amounts of water).
- Take study capsules with 8 ounces of water (capsules are to be swallowed, not chewed).
- Complete the information below for each day

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date							

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Did you take your capsules today?	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No
What time?	_____ am / pm	_____ am / pm	_____ am / pm	_____ am / pm	_____ am / pm	_____ am / pm	_____ am / pm

Temperature:

- Take your oral temperature each day at approximately the same time and record.
- Ensure no recent (within 30 minutes) drinking of hot or cold beverage or smoking.
- If you did not take your temperature, circle Did not take my temperature today

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
What was your temperature today?	°F	°F	°F	°F	°F	°F	°F
	or	*or*	*or*	*or*	*or*	*or*	*or*
	Did not take my temperature today	Did not take my temperature today	Did not take my temperature today	Did not take my temperature today	Did not take my temperature today	Did not take my temperature today	Did not take my temperature today

If you have any questions or concerns
Contact Study Team/Research Nurse/Study Doctor at_____
Completed by: Participant Signature _____ Date_____
Reviewed by: Study Personnel Signature _____ Date_____

Site Number: _____ Participant Study Number: _____

PICI0014 Participant Diary

Study Period: **SER-401/Placebo with Nivolumab Cycle __ Week __**
(page 2)

Bring this diary to your next clinic visit.

Side Effects: Each Day (circle) the most severe intensity for each symptom that you experienced on a day:
0 = **no symptom**
1 = **mild**: I noticed the symptom. It did not keep me from going about my normal activities.
2 = **moderate**: I noticed the symptom and it kept me from doing some of my normal activities.
3 = **severe**: I noticed the symptom and it kept me from doing activities that I really needed and wanted to do.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Gas or flatulence	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3
Abdominal discomfort (distention, bloating, pain or cramping)	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3
Vomiting	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3
Constipation	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3

Diarrhea: If you have diarrhea any day, (circle) the severity in the table below:
None
Mild = 3-4 unformed bowel movements per day
Moderate = 5-6 unformed bowel movements per day
Severe = 7 or more unformed bowel movements per day
Call your study doctor if you experience severe diarrhea for more than 2 days in a row

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Diarrhea	None	None	None	None	None	None	None
	Mild	Mild	Mild	Mild	Mild	Mild	Mild
	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
	Severe	Severe	Severe	Severe	Severe	Severe	Severe

If you have any questions or concerns
Contact Study Team/Research Nurse/Study Doctor at_____
Completed by: Participant Signature _____ Date_____
Reviewed by: Study Personnel Signature _____ Date_____

Site Number: _____ Participant Study Number: _____

PICI0014 Participant Diary

Study Period: **FMT/Placebo with Nivolumab Cycle ___ Week ___**

Bring this diary to your next clinic visit.

Temperature:

- Take your oral temperature each day at approximately the same time and record.
- Ensure no recent (within 30 minutes) drinking of hot or cold beverage or smoking.
- If you did not take your temperature, circle Did not take my temperature today

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
What was your temperature today?	°F	°F	°F	°F	°F	°F	°F
	or	*or*	*or*	*or*	*or*	*or*	*or*
	Did not take my temperature today	Did not take my temperature today	Did not take my temperature today	Did not take my temperature today	Did not take my temperature today	Did not take my temperature today	Did not take my temperature today

Side Effects: Each Day circle the most severe intensity for each symptom that you experienced on a day:
0 = **no symptom**
1 = **mild**: I noticed the symptom. It did not keep me from going about my normal activities.
2 = **moderate**: I noticed the symptom and it kept me from doing some of my normal activities.
3 = **severe**: I noticed the symptom and it kept me from doing activities that I really needed and wanted to do.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Gas or flatulence	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3
Abdominal discomfort (distention, bloating, pain or cramping)	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3
Vomiting	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3
Constipation	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3

If you have any questions or concerns
Contact Study Team/Research Nurse/Study Doctor at_____
Completed by: Participant Signature _____ Date_____
Reviewed by: Study Personnel Signature _____ Date_____

Site Number: _____ Participant Study Number: _____

PICI0014 Participant Diary

Study Period: **FMT/Placebo with Nivolumab Cycle ___ Week ___**
(page 2)

Diarrhea: If you have diarrhea any day, circle the severity in the table below:
None
Mild = 3-4 unformed bowel movements per day
Moderate = 5-6 unformed bowel movements per day
Severe = 7 or more unformed bowel movements per day
Call your study doctor if you experience severe diarrhea for more than 2 days in a row

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Diarrhea	None	None	None	None	None	None	None
	Mild	Mild	Mild	Mild	Mild	Mild	Mild
	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
	Severe	Severe	Severe	Severe	Severe	Severe	Severe

If you have any questions or concerns
Contact Study Team/Research Nurse/Study Doctor at_____
Completed by: Participant Signature _____ Date_____
Reviewed by: Study Personnel Signature _____ Date_____

10.9 APPENDIX 9: LIST OF ABBREVIATIONS

Abbreviation	Definition
ABX	antibiotic
AE(s)	adverse event(s)
AESI(s)	AE(s) of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CBC	complete blood count
CDI	Clostridium difficile infection
cfDNA	cell-free deoxyribonucleic acid
CFU	colony forming unit
cHL	classical Hodgkin lymphoma
CI(s)	confidence interval(s)
CIOMS	Council for International Organizations of Medical Sciences
COA	clinical outcome assessment
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRC	colorectal cancer
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DCR	disease control rate
dMMR	mismatch repair deficient
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ED	early discontinuation
EDC	electronic data collection
EOT	end of treatment
FMT	fecal microbiota transplant; fecal microbiota transplantation
GCP	Good Clinical Practice
GI	gastrointestinal
HCC	hepatocellular carcinoma
HIPAA	Health Insurance Portability and Accountability Act

Abbreviation	Definition
HRT	hormone replacement therapy
Hx	history
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
ICF	informed consent form
ICH	International Council for Harmonisation
I/E	inclusion/exclusion
IHC	immunohistochemistry
IND	Investigational New Drug
irAE(s)	immune-related AE(s)
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ITT	intent-to-treat
IV	intravenous(ly)
IWRS	Interactive Web Response System
LDH	lactate dehydrogenase
MDACC	The University of Texas MD Anderson Cancer Center
MedDRA	Medical Dictionary for Regulatory Activities
MGH	Massachusetts General Hospital
MSI-H	microsatellite instability-high
N	number
NCI	National Cancer Institute
NR	non-responder
NSAID(s)	nonsteroidal anti-inflammatory drug(s)
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
OTU	operational taxonimic unit
PBMC	peripheral blood mononuclear cell
PBO	placebo
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PE	physical exam
PET	positron emission tomography
PFS	progression-free survival
PI	Principal Investigator
PO	orally

Abbreviation	Definition
PR	partial response
PRO	patient reported outcome
Q3M	every 3 months
Q4W	every 4 weeks
QD	daily
QID	four times daily
QOD	every other day
QW	every week
R	responders
RBC	red blood cell
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SCCHN	squamous cell carcinoma of the head and neck
SCFU	spore colony forming unit
SD	stable disease
SER-401	Seres Therapeutics investigational product
SJS	Stevens-Johnson syndrome
SporQs	spore equivalents
SUSAR	suspected unexpected serious adverse reaction
TC-99m	technetium-99m
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
TOC	Table of Contents
TOX	trial-limiting toxicities
TSH	thyroid-stimulating hormone
UC	ulcerative colitis
ULN	upper limit of normal
vs	versus
WBC	white blood cell
WKS	weeks
WOCBP	woman of childbearing potential

10.10 APPENDIX 10: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

DOCUMENT HISTORY	
Documents	**Date of Issue**
Amendment 2	08 Jan 2020
Amendment 1	14 Nov 2018
Original Protocol	25 Sep 2018

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