PARKER INSTITUTE FOR CANCER IMMUNOTHERAPY

Statistical Analysis Plan for

Protocol Number: PICI0014

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

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2 INTRODUCTION

The purpose of this document is to provide details of the planned clinical analyses for PICI0014. The analyses specified in this document supersede the high-level analysis plan described in the protocol and its appendices. Statistical analyses will be performed consistent with the principles of the ICH/FDA Guidance for Industry E9 Statistical Principles for Clinical Trials.

3 STUDY DESIGN

PICI0014 is a Phase 1b, multicenter study in adult participants with unresectable or metastatic melanoma to evaluate the safety, tolerability, and clinical activity of a microbiome study intervention (FMT, SER-401, or matching placebo) in combination with anti-PD-1 therapy (nivolumab) in participants who are naïve to, or recurred following adjuvant completion of, anti-PD-1 therapy. This study is randomized, placebo-controlled, and blinded to the investigators and participants. Participants must have measurable disease that can be biopsied and consent to baseline and on-treatment biopsies.

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 who are 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 open-label SER-401 and anti-PD-1 (nivolumab) treatment as part of a cross-over.

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 group will enroll at least 60% of participants with low *Ruminococcaceae*.

The 2-week antibiotic/microbiome study intervention lead-in phase of the study will consist of 4 days of pretreatment with oral vancomycin or placebo. 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.

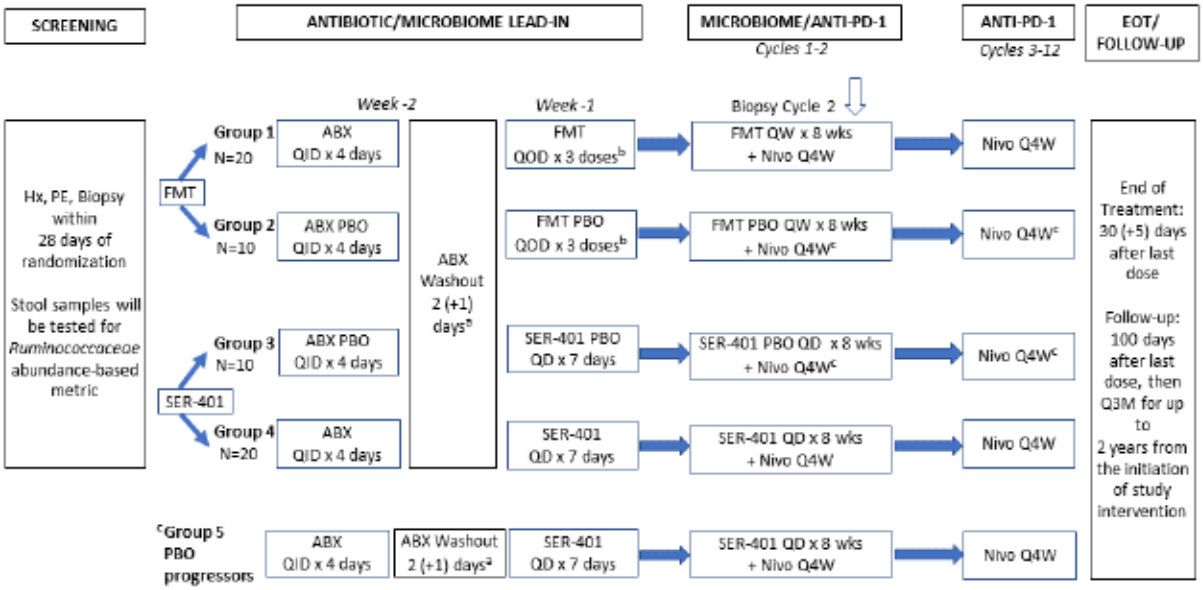
A 1-week loading regimen of the microbiome study intervention will be performed 2-3 days following antibiotic/placebo administration.

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. A treatment cycle will be defined as 4 calendar weeks, starting on the day of each nivolumab infusion. Nivolumab therapy will continue for up to 12 cycles, unless the participant experiences disease progression or unacceptable toxicity in the judgment of the treating physician. During Cycles 1 and 2, participants will receive microbiome study intervention (FMT, SER-401, or placebo) in addition to nivolumab. Beginning at Cycle 3, participants will only receive nivolumab. Participants will be followed for up to 2 years from the time of the initiation of study intervention.

The general study schema is depicted in Figure 1.

In March 2021, the Sponsor decided to terminate the study prior to any participant enrollment into the FMT portion of the study (Groups 1 and 2). In addition, no participants assigned to the placebo arm received open-label SER-401 and nivolumab treatment as part of a cross-over after disease progression. Therefore, this Statistical Analysis Plan will only describe analysis of Groups 3 (SER-401 matching placebo) and 4 (SER-401).

Figure 1: Study Schema



ABX = antibiotic (vancomycin); EOT = end of treatment; FMT = fecal microbiota transplant; Hx = history; Nivo = nivolumab; PBO = placebo; PD-1 = programmed cell death-1; 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

3.1 Protocol Synopsis

The Protocol Synopsis is included in Section 8.1. The schedule of assessments is included in Section 8.2.

3.2 Study Objectives and Endpoints

The study objectives and endpoints are listed in Table 1.

Table 1: 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], overall survival [OS], and duration of response [DOR]). • 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 or baseline microbiome profile. • 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 the 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 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 the date of first 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 from baseline in the percentage of CD8 cells in tumor tissue 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 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; 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

3.3 Determination of Sample Size

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 (CIs) to aid the design of future studies. A sample size of approximately 20 participants per group (vancomycin + FMT + nivolumab, vancomycin + SER-401 + nivolumab, and vancomycin placebo + FMT/SER-401 placebo + nivolumab) will provide these preliminary estimates while limiting exposure.

Table 2 provides 95% confidence intervals for the 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 2: 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

3.4 Analysis Timing

The Sponsor has decided to terminate the study prior to participant enrollment into the FMT portion of the study (Groups 1 and 2). Therefore, this Statistical Analysis Plan will only describe analysis of Groups 3 (vancomycin placebo + SER-401 placebo + nivolumab) and 4 (vancomycin + SER-401 + nivolumab).

The analysis of complete data for the study, described in the main body of this document, will be performed after all participants have either completed the safety and survival follow-up periods or have discontinued early from the study, all data from the study are entered in the clinical database, and the clinical database is locked. The Sponsor may choose to discontinue survival follow-up and close the study at any time.

Ongoing monitoring of safety and efficacy will be performed throughout the study. Details about these cumulative data reviews are presented in Section 4.4. Aggregate results of a cumulative data review, summarized by treatment arm and potentially biomarker subgroup, may be presented and/or published before completion of the study. However, study participants and site personnel will remain blinded to individual treatment assignment until after the study is completed, the database is locked, and the study analyses are final.

4 STUDY CONDUCT

4.1 Intervention Assignment

Participants who are naïve to anti-PD-1 therapy or have recurred following completion of adjuvant anti-PD-1 therapy will be randomly allocated (in a 2:1 ratio) to blinded SER-401 microbiome study intervention (Group 4) or matching placebo (Group 3) using an Interactive Web Response System (IWRS). Randomization will be stratified by fecal microbiome

composition of *Ruminococcaceae* at screening: high (ie, "favorable") or low (ie, "unfavorable"). Each study intervention group will enroll at least 60% of participants with low *Ruminococcaceae*.

4.2 Blinding

Nivolumab will be administered open label to all groups.

Participants will be randomly assigned in a 2:1 ratio to SER-401 or matching placebo. Investigators, site personnel, and participants will remain blinded to the assignment of microbiome study intervention throughout the course of the study. Sponsor personnel who are members of the Data Monitoring Committee (DMC) will be unblinded to treatment assignment for ongoing safety monitoring. In addition, at the time of any cumulative data review, select personnel from the Sponsor and pharmaceutical partners who are responsible for performing and interpreting the analysis results will have full access to unblinded data.

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 whether unblinding of a participant's intervention assignment is warranted. If a participant has radiographic evidence of progression of disease while on study, the Investigator will be able to unblind the participant's intervention assignment. If the participant was allocated to the placebo group (Group 3), the participant may be offered the option to receive open-label SER-401 and nivolumab treatment.

4.3 Safety Data Monitoring

To ensure careful review of the accumulating safety data for the PICI0014 study, a Data Monitoring Committee (DMC) will be established.

Ongoing safety data review will be conducted by the 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 Pharmacovigilance. 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 are 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.

A Bayesian rule will be employed to monitor toxicity throughout the study. 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 in the protocol) is greater than or equal to the number in Table 3, 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 3: 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

4.4 Cumulative Data Reviews

Given the hypothesis-generating nature of this study, all study data, including efficacy, safety, and engraftment data, may be reviewed periodically as part of a cumulative data review. Prior to conducting a cumulative data review, a Memo will be filed in the study Trial Master File (TMF) detailing the timing and scope of the analysis. All analyses will be performed and interpreted by members of the Sponsor and/or pharmaceutical partners of this study. Access to treatment assignment information will follow the Sponsor's standard procedures. If warranted, interim safety and efficacy results may be shared with study Investigators if the results will not unblind the Investigators to participant-level treatment assignments.

Due to the exploratory nature of this study, effect sizes and CIs will not be adjusted to account for ongoing review of data. No stopping rules for futility or positive efficacy will be pre-specified. The results from cumulative data review could result in modifying or stopping a study intervention group(s) based on the risk-benefit profile.

A cumulative data review of efficacy data occurred in September 2020, after 10 participants were randomized into Groups 3 and 4 and followed for at least 6 months. Safety, efficacy (e.g. ORR, DCR, PFS, OS), engraftment, and available biomarker data were analyzed. The analysis was performed and interpreted by personnel from the Sponsor (PICI) and pharmaceutical partner (Seres Therapeutics), who had full access to unblinded data. The timing, scope, and analysis details of this cumulative data review were pre-specified in a Memo that has been filed in the study TMF.

5 STATISTICAL ANALYSIS

The Sponsor has decided to terminate the study prior to participant enrollment into the FMT portion of the study (Groups 1 and 2). In addition, no participants assigned to the placebo arm received open-label SER-401 and nivolumab treatment as part of a cross-over after disease progression. Therefore, this Statistical Analysis Plan will only describe analysis of Groups 3 (vancomycin placebo + SER-401 placebo + nivolumab) and 4 (vancomycin + SER-401 + nivolumab).

Summary statistics will be presented by study intervention group. Categorical variables will be summarized using frequencies and percentages. Continuous variables will be summarized using means, standard deviations, medians, minimums, and maximums.

5.1 Populations for Analysis

5.1.1 Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population will serve as the primary analysis population for all efficacy analyses. The mITT population consists of all participants randomly assigned to Groups 3 or 4 who receive at least 1 dose of any study intervention (vancomycin, SER-401, nivolumab or placebo). Participants will be analyzed according to the study intervention to which they were allocated.

5.1.2 Safety Population

The safety population will serve as the primary analysis population for all safety analyses. The safety population consists of all participants who receive at least 1 dose of any study intervention (vancomycin, SER-401, nivolumab or placebo). Participants will be analyzed according to the study intervention they actually received.

5.2 Analysis of Study Conduct

The number of participants who were randomized, treated, and completed the study will be presented in summary tables. The reason for treatment discontinuation and study discontinuation will be summarized in a table.

5.3 Analysis of Baseline Characteristics

Demographic and baseline characteristics of the study population will be summarized overall and for each study intervention group. Variables to be summarized include, but are not limited to, age, sex, race, ethnicity, Eastern Cooperative Oncology Group (ECOG) performance status, stage at initial diagnosis and study enrollment, and fecal microbiome composition of the *Ruminococcaceae* abundance-based metric at screening (high, low).

The baseline value of any variable will be defined as the last value recorded prior to the first administration of study intervention.

5.4 Efficacy Analysis

Efficacy analyses will be performed on the mITT population, defined as all randomized participants who receive at least 1 dose of any study intervention. Participants will be analyzed according to the study intervention to which they were allocated.

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.

5.4.1 Primary Efficacy Endpoint

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

5.4.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and duration of response (DOR).

5.4.2.1 Objective Response Rate

Objective Response Rate (ORR), on the basis of investigator assessment, is defined as the proportion of participants who attain a best overall response of complete response (CR) or partial response (PR), as determined by RECIST version 1.1 (Eisenhauer, 2009). Confirmation of response by a repeat tumor assessment is not required for a best overall response of CR or PR. Participants without a post-baseline tumor assessment will be considered non-responders, as well as patients with a best overall response of stable disease (SD), progressive disease (PD) or not evaluable (NE).

Response rates for ORR will be estimated within each study intervention group and 95% CIs will be estimated using the Clopper-Pearson method.

Spider plots and waterfall plots will be generated to visualize changes in the sum of target lesions.

5.4.2.2 Disease Control Rate

Disease Control Rate (DCR) is defined as the proportion of participants with a best overall response of (1) CR, (2) PR, or (3) SD lasting at least 24 weeks. The duration of SD is defined as the time from randomization until the date of radiographic disease progression per RECIST version 1.1. If no radiographic progression has occurred and the most recent tumor assessment

with overall response of SD occurred within 24 weeks of randomization, the participant will not have met the SD duration criterion and will not be considered a DCR responder.

Response rates for DCR will be estimated within each study intervention group and 95% CIs will be estimated using the Clopper-Pearson method.

5.4.2.3 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the time from randomization to the date of first documented radiographic progression of disease or date of death due to any cause, whichever occurs first. Participants who continue treatment beyond initial disease progression will be considered to have progression of disease (PD) at the time of the initial progression event.

Participants who do not have radiographic PD at the time of analysis will be censored as follows:

- Participants who do not have radiographic PD and are still on study at the time of analysis will be censored at the date of the last tumor assessment documenting absence of progressive disease.
- Participants who have discontinued study treatment and have started subsequent anti-cancer therapy or had subsequent cancer surgery or radiation prior to documentation of radiographic PD will be censored at the date of the last evaluable tumor assessment prior to the initiation of subsequent treatment.
- Participants who discontinued the study prior to documentation of radiographic PD will be censored at the date of the last tumor assessment documenting absence of progressive disease.
- Participants who do not have radiographic PD and who die more than 16 weeks from their last evaluable tumor assessment will be censored at the date of the last tumor assessment documenting absence of progressive disease. Participants who die within 16 weeks of their last evaluable tumor assessment will be considered as having an event at the date of death.

PFS will be estimated using Kaplan-Meier techniques, and the median survival time and 95% CIs will be estimated within each study intervention group. If median survival is not reached, survival times and 95% CIs will be reported at deciles that are estimable given the observed events. In addition, the 1-year PFS rate will be estimated within each study intervention group and 95% CIs will be estimated using the Clopper-Pearson method.

5.4.2.4 Overall Survival

Overall Survival (OS) is defined as the time from randomization until death due to any cause. Participants who are not reported as having died at the time of analysis will be censored at the most recent contact date they were known to be alive. See Section 5.7.2 for handling of missing or partial death dates.

OS will be estimated using Kaplan-Meier techniques, and the median survival time and 95% CIs will be estimated within each study intervention group. If median survival is not reached, survival times and 95% CIs will be reported at deciles that are estimable given the observed events. In addition, the 1-year OS rate will be estimated within each study intervention group and 95% CIs will be estimated using the Clopper-Pearson method.

5.4.2.5 Duration of Response

For participants who experienced an objective response (CR or PR) during the study, DOR is defined as the time from the first tumor assessment that documents response (CR or PR, whichever is recorded first) to the first documentation of radiographic PD per RECIST version 1.1 or death due to any cause, whichever occurs first.

Participants who have not progressed at the time of analysis will be censored as follows:

- Participants who do not have radiographic PD and are still on study at the time of analysis will be censored at the date of the last tumor assessment documenting response.
- Participants who have discontinued study treatment and have started subsequent anti-cancer therapy or had subsequent cancer surgery or radiation prior to documentation of radiographic PD will be censored at the date of the last tumor assessment documenting response that occurred prior to the initiation of subsequent treatment.
- Participants who discontinued the study prior to documentation of radiographic PD will be censored at the date of the last tumor assessment documenting response.
- Participants who do not have radiographic PD and who die more than 16 weeks from their last evaluable tumor assessment will be censored at the date of the last tumor assessment documenting response. Participants who die within 16 weeks of their last evaluable tumor assessment will be considered as having an event at the date of death.

DOR will be estimated using Kaplan-Meier techniques, and the median DOR and 95% CIs will be estimated within each study intervention group. If median DOR is not reached, duration times and 95% CIs will be reported at deciles that are estimable given the observed events.

5.4.3 Exploratory Efficacy Endpoints

Exploratory clinical efficacy endpoints for this study include ORR, DCR, PFS, and OS in participants who receive open-label SER-401 after progressing while on placebo. These endpoints will not be analyzed as no study participants assigned to the placebo arm received open-label SER-401 and nivolumab treatment as part of a cross-over after disease progression.

5.4.4 Sensitivity Analyses

The following sensitivity analyses may be performed:

- ORR and DCR, requiring confirmation of response (CR/PR) by a repeat tumor assessment performed no less than 4 weeks after the criteria for initial radiographic response were first met, will be estimated within each study group and 95% CIs will be presented.

5.4.5 Subgroup Analyses

Results for efficacy endpoints may be presented for the following subgroups:

- *Ruminococcaceae* abundance-based metric at screening (high, low).
- Prior anti-PD-1 therapy received (yes, no).
- Presence of liver metastases, as target or non-target lesion(s) (yes, no).
- Tumor burden at screening, defined as the sum of the diameters of all target lesions.

5.5 Biomarker Analysis

Secondary biomarker endpoints include:

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

Analysis details of the engraftment endpoint will be described in a separate Microbiome SAP.

Descriptive statistics will be used to evaluate the percentage of CD8 cells at each timepoint by study intervention group. CD8 changes from baseline will be plotted and summarized at each timepoint by study intervention group.

The exploratory biomarker endpoints include:

- Changes in the composition of the fecal microbiome from baseline to on treatment.
- 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.

Biomarker exploratory analyses will be determined based on study outcomes and further described in a Translational Analysis Plan and/or Microbiome SAP.

5.6 Safety Analysis

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, SER-401, nivolumab, or placebo). Participants will be analyzed according to the study intervention they actually received.

Safety will be assessed through summaries of AEs, clinical laboratory test results, vital signs, ECGs, and ECOG performance status.

5.6.1 Exposure to Study Medication

The number of participants exposed to each study intervention and the extent of exposure (as number of doses and cumulative dose received, as applicable) will be summarized by study intervention group using descriptive statistics.

5.6.2 Adverse Events

All reported AEs will be coded using a recent version of the Medical Dictionary for Regulatory Activities (MedDRA) and graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

A treatment-emergent adverse event (TEAE) is defined as any event that either occurs after the initiation of study intervention, 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 study intervention. AEs assessed by the Investigator to be 'Possibly', 'Probably', or 'Definitely' related to any study intervention, as well as AEs with missing relationship, will be considered treatment related.

Handling of missing and partial-missing AE dates is described in Section 5.7.1.

The incidence of AEs will be summarized by study intervention group for the following categories:

- All TEAEs

- All treatment-related AEs (TRAEs)
- Grade 3-4 TEAEs and TRAEs
- Serious adverse events (SAEs)
- AESIs
- Deaths due to an AE
- AEs leading to treatment discontinuation

Treatment-emergent and treatment-related AEs will also be summarized by coded preferred term and system organ class by study intervention group. In addition, separate summaries will be generated for AESIs and SAEs.

The following listings will be generated:

- TEAEs
- TRAEs
- SAEs
- Grade 3-4 TEAEs
- Grade 3-4 TRAEs
- AESIs
- AEs leading to treatment discontinuation
- Deaths, including primary cause of death

5.6.3 Laboratory Data

Clinical laboratory findings will be summarized by the proportion of participants with on-treatment values outside the normal range for each study intervention group.

Select laboratory tests (including but not limited to alanine aminotransferase, albumin, alkaline phosphatase, calcium, creatinine, hemoglobin, lactate dehydrogenase, and platelet count) will be graded according to CTCAE version 5.0, and the highest grade per laboratory test per participant will be summarized by study intervention group.

5.6.4 Vital Signs

Vital signs at each visit and change from baseline to each visit will be summarized using descriptive statistics for each study intervention group. The baseline value of any variable will be defined as the last value recorded prior to the first administration of study intervention. Participants with a missing baseline value will not be summarized for that variable.

5.6.5 Physical Examinations

Physical examination data will not be summarized because any significant finding will be reported and summarized as an AE.

5.7 Missing Data

5.7.1 Missing and Partial Missing Adverse Event Dates

If the AE start date is not a complete date, the following rules will be applied to determine whether the event is treatment emergent.

- If the start date is completely missing: The AE will be considered treatment emergent unless the AE stop date is earlier than the date of first dose of study intervention.
- If the day of the AE start date is missing:
    - If the month and year of the start date are later than the month and year of the date of first dose of study intervention, then the AE will be considered treatment emergent.
    - If the month and year of the start date are equal to the month and year of the date of first dose of study intervention and the stop date is unknown or later than the date of first dose of study intervention, then the AE will be considered treatment emergent.
- If the day and month of the start date are missing:
    - If the year of the start date is later than the year of the date of first dose of study intervention, then the AE will be considered treatment emergent.
    - If the year of the start date is equal to the year of the date of first dose of study intervention and the stop date is unknown or later than the date of first dose of study intervention, then the AE will be considered treatment emergent.

5.7.2 Missing and Partial Missing Death Dates

For death dates, the following conventions will be used for imputing partial dates:

- If the date of death is completely or partially missing, but there is an AE with the outcome as 'Fatal', the date of death will be replaced by the end date of the AE.
- If only the day of the month is missing and there is no AE with outcome as 'Fatal', the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known date alive plus 1 day, and the maximum will be considered as the death date.
- If the month or the year is missing, the death date will be imputed as the last known date alive plus 1 day.
- If the date is completely missing but the reason for death is present, the death date will be imputed as the last known date alive plus 1 day.

6 DIFFERENCES COMPARED TO PROTOCOL

The following list provides a high-level overview of the differences between the SAP and the Protocol.

- Section 4.4 (Cumulative Data Reviews)
    - The SAP introduces the concept and describes the details of cumulative data reviews.
- Section 5.1 (Populations for Analysis)
    - The SAP defines the modified Intent-to-Treat (mITT) population, which will be used for all efficacy analyses.
- Section 5.4 (Efficacy Analysis)
    - The protocol states that efficacy analyses will be performed on the Intent-to-Treat (ITT) and Efficacy Populations. The SAP clarifies that efficacy analyses will be performed on the mITT Population.
- Section 5.6 (Safety Analysis)
    - The protocol states that safety analyses will be performed on the Safety Population, Anti-PD-1 Safety Population, Antibiotic Safety Population, and the Microbiome Safety Population. The SAP clarifies that safety analyses will only be performed on the Safety Population.

7 REFERENCES

1. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford, R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

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8 APPENDICES

8.1 Protocol 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: Melanoma Checkpoint and Gut Microbiome Alteration with 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 disease or date of death due to any cause, whichever occurs first.

Objectives	Endpoints
	• 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

8.2 Schedule of Assessments

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								

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
Collection of participant-reported diary[l]		X	X	X	X	X				
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.

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