PARKER INSTITUTE
for CANCER IMMUNOTHERAPY

Statistical Analysis Plan

Protocol Number: PICI0001

Protocol Title: A Randomized, Phase 2 Study of Ipilimumab Vs Ipilimumab plus Nivolumab in Patients with Stage III-IV Melanoma Who Have Progressed or Relapsed on PD-1 Inhibitor Therapy

NCT Number:	NCT02731729
Sponsor:	Parker Institute for Cancer Immunotherapy (PICI) 1 Letterman Drive Suite D3500 San Francisco, CA 94129 Tel: 415-985-7311 Fax: 415-872-5305
Date Final	12-APR-2019

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IND Number:	Not Applicable
Name of Products:	Ipilimumab and Nivolumab
Phase of Development:	2
Indication:	Stage III-IV Melanoma
Sponsor:	Parker Institute for Cancer Immunotherapy 1 Letterman Drive, Suite D3500 San Francisco, CA 94129 Tel: 415-985-7311 Fax: 415-872-5305
Date Final:	12-APR-2019

SPONSOR APPROVAL PAGE

Christopher Cabanski, PhD
Senior Biostatistician

Date: 16-Apr-2019

Ramy Ibrahim, MD
Vice President, Clinical Development

Date: 18APR2019

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2 INTRODUCTION

The purpose of this document is to provide details of the planned analyses for Study PICI0001. The primary analyses described in the main body of this document will be performed after all participants have completed the 2-year follow-up period in the study or discontinued early, and all corresponding data have been entered into the database, reviewed, and verified and the database locked. No changes to the SAP will be allowed at the time of or subsequent to database lock.

The analyses specified in this document supersede the high-level analysis plan described in the protocol.

Statistical analyses will be performed using SAS or R statistical software.

3 STUDY DESIGN

Study PICI0001 is a multi-center, randomized, Phase 2 study of ipilimumab vs ipilimumab plus nivolumab in participants with unresectable Stage III or Stage IV melanoma who were refractory to PD-1 inhibitor monotherapy.

There will be two treatment arms in this study:

Arm A: Participants will receive combination checkpoint blockade with ipilimumab and nivolumab.

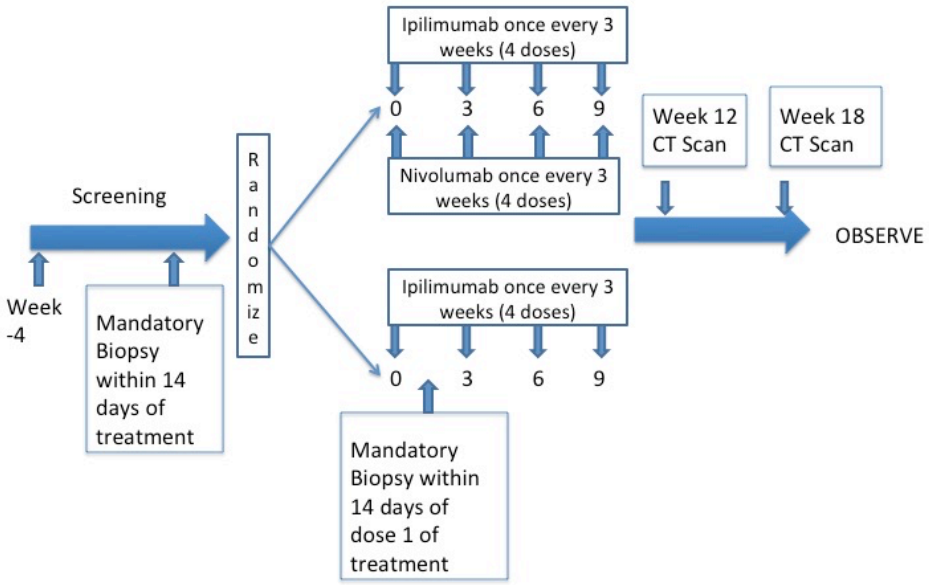
Arm B: Participants will receive ipilimumab alone.

Participants who are eligible will be required to have a pre-treatment biopsy and then will be randomized to either ipilimumab alone or ipilimumab in combination with nivolumab. Participants will receive treatment for up to 4 cycles followed by an observation phase.

The primary objective is to determine the response rate of combination ipilimumab/nivolumab and ipilimumab alone in participants previously treated with a PD-1 inhibitor by Week 18 of therapy. The total planned enrollment is 24 total participants, with 12 participants randomly allocated to each arm. Participants will be assessed for the primary endpoint at Week 18. They will then be followed for time to treatment failure (TTF) and overall survival (OS) for up to 2 years.

The study design is depicted in Figure 1.

Figure 1: Study Schema



Note: The on-treatment biopsy has a window of ±5 days.

3.1 Protocol Synopsis

The Protocol Synopsis is included as Appendix 1. The Schedule of Assessments is included as Appendix 2.

3.2 Study Objectives

3.2.1 Primary Objective

The primary objective is to assess response rates of combination ipilimumab/nivolumab and ipilimumab alone in participants previously treated with a PD-1 inhibitor by Week 18 of therapy.

3.2.2 Secondary Objectives

The secondary objectives are:

- To assess clinical benefit of combination ipilimumab/nivolumab and ipilimumab alone.
- To evaluate time to treatment failure (TTF) and overall survival (OS) for each arm.
- To assess safety and tolerability of ipilimumab alone and in combination with nivolumab in previously treated participants.

3.2.3 Exploratory Objectives

The exploratory objectives for this study are listed in Appendix 1.

3.3 Study Endpoints

3.3.1 Primary Endpoint

The primary endpoint is the response to ipilimumab/nivolumab and ipilimumab alone by Week 18, defined as having achieved a complete response (CR) or partial response (PR) as measured by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria or a PR/CR at any time prior to Week 18.

3.3.2 Secondary Endpoints

The secondary endpoints are:

- The disease control rate (DCR) by RECIST v1.1 criteria of overall tumor burden at Week 12, where DCR is defined as participants who achieve stable disease (SD), PR, or CR.
- DCR at Week 18, where DCR is defined as participants who achieve SD, PR, or CR.
- TTF up to two years, where TTF is defined as the time from first study drug treatment until the participant is started on another line of systemic therapy or participant death, whichever occurs first. Participants who are alive and do not start another therapy will be censored at the time of last follow-up.
- OS up to two years, where OS is defined as the time from first study drug treatment until death from any cause. Participants without documentation of death will be censored on the date of last contact.
- Safety and tolerability, as measured by:
    - Incidence and severity of adverse events, with severity determined through the use of the Common Terminology Criteria for Adverse Events (CTCAE) v4.0.
    - Change from baseline in physical examination findings, vital signs, and clinical laboratory results.

3.3.3 Exploratory Endpoints

The exploratory endpoints for this study are listed in Appendix 1.

3.4 Determination of Sample Size

This study is not intended or powered for hypothesis testing. The study is intended to provide preliminary estimates of adverse events, response rates, effect sizes and confidence intervals. A sample size of approximately twelve participants in each arm, for a total of 24 participants, will provide these preliminary estimates. The study protocol incorrectly states that a Simon 2-stage design will be implemented for this study. A 2-stage design was not implemented; rather, a single-stage design was used.

Table 1 provides 95% exact confidence intervals for the proportion of responders per treatment arm. These confidence intervals provide information needed for the design of future studies.

Table 1: Confidence Intervals for the True Proportion of Responders

Observed responder rate	95% Confidence Interval (n = 12)
8.3% (1/12)	(0.2%, 38.5%)
16.7% (2/12)	(2.1%, 48.4%)
25.0% (3/12)	(5.5%, 57.2%)
33.3% (4/12)	(9.9%, 65.1%)

41.7% (5/12)	(15.2%, 72.3%)
50.0% (6/12)	(21.1%, 78.9%)

3.5 Analysis Timing

The analysis of complete data for the study, including data from the follow-up period, will be performed when all participants have either (i) completed two years of follow-up, (ii) discontinued early from the study, or (iii) died, and all data from the study are in the database and the database is locked.

4 STUDY CONDUCT

4.1 Randomization Details

Randomization will be managed centrally using an interactive voice response system (IVRS). Participants will be randomized following their pre-treatment biopsy at the Screening/Baseline Visit. Participants will be stratified based on their previous response to PD-1 therapy.

4.2 Data Monitoring

The study will be closely monitored, and data will be reviewed on an ongoing basis. In order to ensure the safety and well-being of participating subjects, as well as the validity of data during the study, a Data Review Team (DRT) will review the safety and further emerging data on a regular basis. During these meetings, aggregated safety data and individual participant data derived from medical data listing reviews will be presented, reviewed, and discussed. The DRT team will consist of team members from the Sponsor, the Contract Research Organization (CRO), the Coordinating Principal Investigator (PI), and all active PIs.

5 STATISTICAL METHODS

Summary statistics will be presented by treatment arm. For continuous variables, data will be summarized with the number of participants (N), mean, standard deviation, median, minimum, and maximum. For categorical variables, data will be tabulated with the number and proportion of participants for each category.

5.1 Analysis Populations

5.1.1 Efficacy-Evaluable Population

The efficacy-evaluable population will include all participants who were randomly allocated to receive either combination ipilimumab/nivolumab or ipilimumab alone and received at least one dose of any study intervention (ipilimumab or nivolumab). For analyses based on this population, participant treatment groups will be defined according to the treatment that was assigned at randomization (ipilimumab/nivolumab or ipilimumab alone).

5.1.2 Safety-Evaluable Population

The safety-evaluable population, also referred to as the toxicity-evaluable population in the study protocol, will include all participants who received at least one dose of any study intervention (ipilimumab or nivolumab). Note that this is a more conservative definition than

the toxicity-evaluable population defined in the Protocol, which includes all participants who completed at least one cycle on either treatment arm. For analyses based on this population, participant treatment groups will be defined according to the treatment that was assigned at randomization. However, if a participant received the incorrect study drug for the entire period of treatment, the participant's treatment group will be defined as the incorrect drug the participant actually received.

5.2 Analysis of Study Conduct

The number of participants randomized will be tabulated by treatment arm. Participant disposition (the number of participants randomized, receiving at least one cycle of study drug during the treatment period, and completing the 4-cycle treatment period) and time on study will be tabulated by treatment arm. Reasons for premature discontinuation from study treatment and reasons for premature discontinuation from the study, including the 2-year follow-up period, will be summarized.

5.3 Analysis of Treatment Group Comparability

Demographic and baseline characteristics, including but not limited to age, sex, race, ethnicity, melanoma subtype, melanoma disease stage, previous response to anti-PD-1 therapy, time since last anti-PD-1 treatment, baseline Eastern Cooperative Oncology Group (ECOG) performance status, and baseline lactate dehydrogenase (LDH) levels will be summarized for the efficacy-evaluable population by treatment arm using descriptive statistics. The baseline measurement used for the analysis of treatment group comparability is assumed to be from the Baseline/Screening Visit.

5.4 Efficacy Analysis

Efficacy analyses will be conducted on the efficacy-evaluable population (see Section 5.1.1), with participants grouped according to the treatment assigned at randomization.

Per the intention-to-treat principle, data from all randomized and dosed participants, regardless of adherence to study drug or to the protocol, will be included in the efficacy analyses. Efficacy summaries will include data from participants who discontinued study drug early but continued with study assessments and may include data collected at unscheduled visits, early termination visits, or follow-up visits.

Comparisons of Interest

This study is not powered for statistical comparisons between arms.

Type I Error Management

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

Covariate Adjustment

Unless otherwise noted, analyses of primary and secondary efficacy endpoints will be adjusted for the following covariate:

- Previous response to PD-1 therapy (primary refractory disease, progressive disease)

Given that the above covariate is the stratification factor used when randomly allocating participants, no missing data of this baseline covariate is expected.

5.4.1 Primary Efficacy Endpoint

The primary endpoint is the response to ipilimumab/nivolumab and ipilimumab alone by Week 18, defined as having achieved CR or PR as measured by RECIST v1.1 criteria, or a PR/CR at any time prior to Week 18.

The objective response rate (ORR) is defined as the number of participants whose best objective response (BOR) is CR or PR divided by the total number of participants in the population of interest. Participants with a BOR of stable disease (SD), progressive disease (PD) or without a post-baseline tumor assessment will be considered non-responders and, thus, will be counted in the denominator of the ORR calculation.

The BOR is defined as the best response designation, as determined by the investigator, recorded between the date of randomization and the date of subsequent anticancer therapy (including tumor-directed radiotherapy and tumor-directed surgery). For participants without subsequent anticancer therapy, all available response designations through Week 19 (Week 18 +7 day window) will contribute to the BOR assessment.

The ORR will be estimated within each treatment arm and 95% confidence intervals (CIs) will be estimated using the Clopper-Pearson method.

This study is not powered for statistical comparisons between arms. To aid in interpretation, each arm will be indirectly compared to the historical ipilimumab ORR of 10.9% (Hodi et al. 2010).

5.4.2 Secondary Efficacy Endpoints

Disease Control Rate

DCR is defined as the proportion of participants who achieve SD, PR, or CR as measured by RECIST v1.1. That is, DCR is the number of participants whose BOR is SD, PR, or CR divided by the total number of participants in the population of interest. For SD, measurements must have met the SD criteria per RECIST v1.1 at least once after study entry, with disease assessment occurring at least 8 weeks after first study drug treatment.

DCR will be assessed at Week 12 (+7 days) and Week 18 (+7 days). DCR will be estimated within each treatment arm and 95% confidence intervals (CIs) will be estimated using the Clopper-Pearson method.

This study is not powered for statistical comparisons between arms. To aid in interpretation, each arm will be indirectly compared to the historical ipilimumab DCR of 28.5% (Hodi et al. 2010).

Time to Treatment Failure

TTF is defined as the time from first study drug treatment until the participant is started on another line of systemic therapy or participant death, whichever occurs first. Participants who are alive and do not start another therapy will be censored at the date of last follow-up. Time to event distributions will be estimated using Kaplan-Meier techniques.

Overall Survival

OS is defined as the time from first study drug treatment until death from any cause. Participants without documentation of death will be censored on the date of last contact. Time to event distributions will be estimated using Kaplan-Meier techniques.

5.4.3 Exploratory Efficacy Endpoints

Exploratory endpoints defined in the protocol are outside the scope of this SAP.

5.4.4 Sensitivity Analyses

No sensitivity analyses are planned for this study.

5.5 Safety Analysis

Safety will be assessed through the summary of adverse events (AEs), serious adverse events (SAEs), laboratory test results (hematology and serum chemistry), vital signs, and physical examinations. Safety summaries will include endpoints as described in Section 3.3.2. This may include data collected at unscheduled visits, early termination visits, or follow-up visits.

Safety outcomes will be summarized based on the safety-evaluable population (see Section 5.1.2). Safety summaries will be presented by treatment arm.

5.5.1 Exposure of Study Medication

Exposure to study drug will be summarized by treatment arm assigned at randomization.

The number of doses of study drug received will be summarized using descriptive statistics.

5.5.2 Adverse Events

Each AE will be coded using MedDRA dictionary version 19.1 and graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

AEs with relationship to study drug of “Possible”, “Probable”, “Definite”, or unknown (missing) will be considered drug-related.

Treatment-emergent adverse event (TEAE) is defined as an AE occurring on or after Day 1 of study treatment and having been absent pre-treatment or that has worsened relative to the pre-treatment state, and no later than 100 days following the last day of study treatment. Events with an onset prior to Day 1 will constitute pre-treatment events. Any AE deemed related to study drug will also be considered as a TEAE regardless of elapsed time since last study treatment.

Listings for all AEs, SAEs, and TEAEs will be presented. Summaries of treatment-emergent events by treatment arm will be provided for each of the following categories:

- AEs
- AEs by most extreme severity
- AEs assessed as related to study drug by the investigator
- SAEs
- AEs leading to discontinuation of study treatment

In addition, participant deaths and the primary cause of death will be listed, as well as any cases of pregnancy.

5.5.3 Laboratory Data

Routine clinical laboratory findings will be summarized using descriptive statistics for each treatment group. Changes from baseline to each visit will be determined for quantitative variables.

5.5.4 Vital Signs

Vital signs at each visit and change from baseline to each post-baseline visit will be summarized using descriptive statistics for each treatment arm.

5.5.5 Physical Examinations

Physical examination data will not be summarized because any significant findings should be captured and summarized as adverse events.

5.6 Missing Data

5.6.1 Missing and Partial Missing Adverse Event Dates

Partially missing data of AE onset date may be imputed in order to avoid eliminating information from summary tables of TEAEs. If the day of an AE onset date is missing but both the month and year are available, the AE will be flagged as treatment-emergent if the date is conservatively estimated to be within 100 days after the last dose of study drug administration. Any AE deemed related to study drug will also be considered a TEAE regardless of elapsed time since last study drug administration. There will be no attempt to impute missing or partially missing dates for the listing of AEs.

5.6.2 Partial Missing Death Dates

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

- If only the day of the month is missing, 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.

5.6.3 Partial Missing Treatment Failure Dates

For date of treatment failure, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day. In cases where the date of death is present and complete, the imputed treatment failure date will be compared to the date of death. The minimum of the imputed treatment failure date and date of death will be considered as the date of treatment failure.
- If the day and month are missing or a date is completely missing, it will be considered as missing.

5.7 Interim Analyses

No formal interim analysis is planned for this study.

6 DIFFERENCES COMPARED TO PROTOCOL

- Section 3.4 (Determination of Sample Size): SAP provides additional justification for the selection of sample size.
- Section 3.4 (Determination of Sample Size): The study protocol incorrectly states that a Simon 2-stage design will be implemented for this study. The SAP clarifies that a 2-stage design was not implemented.
- Section 5.1.2 (Safety-Evaluable Population): The toxicity-evaluable population referred to in the Protocol has been modified and renamed the safety-evaluable population in the SAP. All safety analyses will be conducted on the safety-evaluable population and not the toxicity-evaluable population.
- Section 5.4.4 (Safety Analysis): Although the Protocol lists physical examination findings as a secondary safety endpoint, physical examination data will not be summarized because any significant findings should be captured and summarized as adverse events.
- Section 6.1.2 (Randomization): Although the protocol states that participants will be stratified based on melanoma subtype, this stratification factor was not implemented into the IVRS. Participants were only stratified on their previous response to PD-1 therapy (primary refractory vs progressive disease).
- Section 12 (Statistical Analysis): SAP clarifies that the statistical analyses may be performed using SAS or R statistical software.

7 REFERENCES

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. The New England journal of medicine. 2010;363(8):711-723.

8 APPENDICES

8.1 Protocol Synopsis

Title of Study:	A Randomized, Phase 2 Study of Ipilimumab vs Ipilimumab plus Nivolumab in Participants with Stage III-IV Melanoma Who Have Progressed or Relapsed on PD-1 Inhibitor Therapy
Protocol Number:	PICI0001
Investigators/Study Sites:	This study will be conducted at multiple sites in the United States.
Phase of Development:	2
Objectives:	**Primary Objectives:** To assess response rates of combination ipilimumab/nivolumab and ipilimumab alone in participants previously treated with a programmed death receptor (PD-1) inhibitor by Week 18 of therapy. **Secondary Objectives:** • To assess clinical benefit of combination ipilimumab/nivolumab and ipilimumab alone • To evaluate time to treatment failure and overall survival (OS) for each arm • To assess safety and tolerability of ipilimumab alone and in combination with nivolumab in previously treated participants **Exploratory Objectives:** • To evaluate peripheral lymphocyte phenotype changes throughout treatment • To evaluate changes in quantities of myeloid derived suppressor cells (MDSCs), defined as CD14+HLA-DR^{low} cells, and T_{reg} cells, defined as CD4+FOX3P+ cells, throughout treatment • To evaluate nCounter immune profiling of the tumor before treatment • To explore tumor neoepitopes and mutational burden via whole gene and exome sequencing on pre-treatment tumor biopsy and correlation with clinical response • To stratify clinical response rate by PD-L1 expression on pre-treatment biopsies • To evaluate the tumor immune microenvironment on pre- and on-treatment tumor biopsies
Study Design:	This is a multi-center, randomized Phase 2 study of ipilimumab vs ipilimumab plus nivolumab in participants previously treated with a PD-1 inhibitor by Week 18 of therapy. There will be 2 arms in the study. **Arm A**: Participants will receive combination checkpoint blockade with ipilimumab and nivolumab. **Arm B**: Participants in this arm will receive ipilimumab alone. A Simon 2-stage design will be implemented in each arm, allowing for early stopping for futility. Participants who are eligible will be required to have a pre-treatment biopsy and then will be randomized to either ipilimumab alone or ipilimumab in combination with nivolumab. Participants will be required to have an on-treatment biopsy within 14±5 days of their first dose of treatment. Participants will receive up to 4 cycles of treatment followed by observation phase. Participants will be assessed for the primary endpoint at 18 weeks and then be followed for time to treatment failure (TTF) and OS for up to 2 years.

Selection of Participants:	Main Inclusion Criteria: 1. AJCC (2009) 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. 2. Measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm with conventional techniques or as >10 mm with computerized tomography (CT) scan. Participants must have at least one measurable lesion by Response Evaluation Criteria in Solid Tumors (RECIST) and a separate lesion amenable to biopsy. 3. Histologic proof of melanoma reviewed and confirmed by the enrolling site. 4. Previous treatment with a PD-1 or PD-L1 inhibitor with documented progression of disease on most recent CT scan. Progression of disease is defined as 1) the appearance of a new measurable lesion (>10 mm) on cross-sectional imaging or physical examination OR 2) enlargement of previously detected lesions on two consecutive imaging studies OR 3) enlargement of a previously detected lesion with correlative symptomatology on one cross-sectional imaging study. Participants remain eligible if they had a previous response to a PD-1 inhibitor, including participants who had a complete response, partial response or stable disease (SD). Any participant who had refractory or relapsed disease is eligible for study enrollment. Treatment populations are defined in Section 12. 5. Participants who received adjuvant PD-1 therapy who then develop measurable disease are eligible. However, they must have received their last dose of PD-1/PD-L1 blockade within two months of enrollment in this study. They will be stratified with participants who have primary progressive disease. 6. Life expectancy of greater than 3 months. 7. Age ≥ 18 years old. 8. Eastern Cooperative Oncology Group performance status = 0 or 1 or Karnofsky Performance Status equivalent. 9. Participants must have adequate organ and marrow function as defined below: a. White blood cells >2, 000/mcL b. Absolute neutrophil count >1,500/mcL c. Platelets >100,000/mcL d. Hemoglobin > 9.0 g/dL e. Total bilirubin ≤ 1.5 X institution's upper limit of normal f. Aspartate aminotransferase (serum glutamic oxaloacetic transaminase)/alanine aminotransferase (serum glutamic pyruvic transaminase) ≤ 2.5 X institution's upper limit of normal for participants with no concurrent liver metastases, OR ≤ 5 X institution's upper limit of normal for participants with concurrent liver metastases g. Serum creatinine < 1.5x OR creatinine clearance of at least 40 10. Women of childbearing potential must have a negative serum pregnancy test within 24 hours prior to the start of study drug. A woman of childbearing potential is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 50 in the absence of other biologic or physiologic causes.

	11. Women with child bearing potential and men with reproductive potential must be willing to practice acceptable methods of contraception. 12. Ability to understand and the willingness to sign a written informed consent document. 13. Willingness to undergo biopsy of metastatic site or site of unresectable disease prior to randomization. Main Exclusion Criteria: 1. Concurrent malignancies: a. Participants with a previously treated malignancy are eligible to participate if all treatment of that malignancy was completed at least 2 years before registration and the participant has no evidence of disease. b. Participants who have a concurrent malignancy that is clinically stable and does not require tumor-directed treatment are eligible to participate if the risk of the prior malignancy interfering with either safety or efficacy endpoints is very low (with agreement from the sponsor and principal investigator). c. Other malignancies may be permitted if the risk of the prior malignancy interfering with either safety or efficacy endpoints is very low (with agreement from the sponsor and principal investigator). 2. Any major surgical procedures or external beam radiotherapy within 14 days prior to study drug administration. 3. Use of other investigational drugs within 28 days prior to study drug administration. 4. Symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression. Treated brain metastases must have been stable for at least 1 month and require treatment with less than 10mg/day prednisone equivalent for at least 2 weeks prior to study drug administration. 5. Prior exposure to either ipilimumab or combined checkpoint blockade. 6. 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. 7. Pregnant women and lactating women. 8. History of uveal melanoma. 9. Known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection (with the exception of chronic or cleared HBV or HCV infection, which will be allowed). Once-documented negative result for HIV, HBV, and HCV is sufficient. 10. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection and psychiatric illness/social situations that would limit compliance with study requirements. 11. Participants with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted.

	12. Participants with history of any grade 4 toxicity during previous anti PD-1 treatment or history of Grade 3 or higher pneumonitis. 13. Participants with a history of Grade ≥2 neuropathy. 14. Prisoners or participants who are involuntarily incarcerated. 15. Children under the age of 18. 16. Participants who require hemodialysis. 17. Participants with a history of allergy to study drug components or history of a severe hypersensitivity reaction to any monoclonal antibody.
Planned Sample Size:	Twelve participants will be enrolled in each arm for a total of 24 participants.
Investigational Therapy:	Not Applicable
Reference Therapy:	Arm A: Nivolumab (1 mg/kg of body weight) in combination with ipilimumab (3 mg/kg), both once every 3 weeks for 4 doses administrated intravenously. Or Arm B: ipilimumab (3 mg/kg) alone, once every 3 weeks for 4 doses administrated intravenously.
Treatment Duration:	Participants on both arms will receive treatment for up to 4 cycles (each cycle is of 21 days±4 days) and then be observed for up to 2 years in the follow up period. Participants will undergo screening and, if eligible, will undergo intervention in the selected arm of the study up to 4 cycles.
Criteria for Evaluation:	Efficacy: Therapeutic response and outcome assessment will be done in this study using the international criteria proposed by the RECIST version 1.1 Committee. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Lesions are either measurable or non-measurable. "Target" and "Non-Target" lesions will be identified and recorded at baseline. Responses will be assessed as follows: • Complete Response (CR): Disappearance of all target and non-target lesions and no evidence of new lesions documented by 2 disease assessments at least 4 weeks apart. • Partial Response (PR): At least a 30% decrease in the in the longest dimension (LD) of all target lesions, taking as reference the baseline sum LD. There can be no unequivocal progression of non-target lesions and no new lesions. Documentation by 2 disease assessments at least 4 weeks apart is required. Progressive Disease (PD): At least a 20% increase in the sum of LD of target lesions, taking as reference the smallest sum LD or the appearance of new lesions within 8 weeks of study entry. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. • Stable Disease (SD): Any condition not meeting the above criteria. • Inevaluable for response is defined as having no repeat tumor assessments following initiation of study therapy for reasons unrelated to symptoms or signs of disease. Outcome will be assessed as follows: • Objective Response Rate (ORR): The proportion of participants with either (1) CR or (2) PR by RECIST 1.1 criteria. • Survival: The observed length of life from first dose of study drug to death or the date of last contact. • Time to treatment failure: Is defined as the time from first study drug treatment until the participant is started on another line of systemic therapy or participant death, whichever occurs first. Participants who

	are alive and do not start another therapy will be censored at the time of last follow-up. Safety: Safety assessments (vital signs, physical examinations, performance status, height/weight, electrocardiogram (ECG) recording, adverse events (AEs), clinical laboratory results (routine hematology and biochemistry, and CT and magnetic resonance imaging [MRI] scans) are to be performed at protocol-specified visits.
Study Endpoints:	Primary endpoints: • The response to combination ipilimumab/nivolumab and ipilimumab alone at Week 18 defined as having achieved a complete response or PR as measured by RECIST 1.1 criteria or a PR/complete response at any time prior to Week 18. Secondary endpoints: • Disease control rate (DCR) by RECIST v1.1 criteria of overall tumor burden at Week 12 and Week 18. DCR is defined as participants who achieve SD, PR or complete response. • TTF and OS up to 2 years. • Safety and tolerability measured via metrics such as laboratory tests, vital signs, physical examinations as well as toxicity as graded by Common Terminology Criteria for Adverse Events v4.0. Exploratory endpoints: • All research samples for exploratory endpoints will be analyzed at a Parker Institute for Cancer Immunotherapy selected testing center. • Peripheral lymphocyte phenotype changes throughout treatment, including T_{reg} cells, defined as CD4+FOX3P+ cells, will be expressed using descriptive statistics at pre and post treatment time points. These will be assessed via flow cytometry of peripheral blood mononuclear cells. • Changes in quantities of MDSCs, defined as CD14+HLA-DR^{low} cells, throughout treatment will be expressed using descriptive statistics at pre and post treatment time points. • nCounter immune profiling of the tumor before treatment will be expressed using descriptive statistics at pre and post treatment time points and will be correlated with clinical response also using logistic regression models. • Tumor neoepitopes and mutational burden will be correlated with clinical response also using logistic regression models. • Summary statistics will be generated and differences between mutation burden or neo-antigen score as they relate to PD-L1 expression • Immunohistochemistry (IHC) will be used to assess PD-L1 expression on both immune cells and tumor cells. PDL-1 expression will be assessed pretreatment and on-treatment. A participant will be PD-L1 + if >1% of cells express PD-L1. If response data permit, the tumor positivity of PD-L1 expression will be compared in the pre- and post-treatment biopsies using a Wilcoxon signed rank test. • Pre- and on- treatment PD-L1 expression and will be correlated with clinical response also using logistic regression models. • IHC will be used to quantify cytotoxic and regulatory T-cells, including stains for CD3, CD4, CD8, FOXP3, inducible co-stimulatory and Lag3. Associations from pre to post treatment will be assessed using the Wilcoxon signed rank test for paired

	comparisons (e.g., the continuous measure, density of cells per high powered field).
Statistical Methods and Planned Analyses:	This is a multi-center, randomized, Phase 2 study of ipilimumab and combined checkpoint blockade with ipilimumab and nivolumab. Randomization will be performed via a central process. In each arm, an optimal Simon 2-stage design will be implemented. A response rate of 10% or less would not be considered promising (null hypothesis) as the ipilimumab response rate in untreated participants is 10.9%. A response rate of at least 30% is promising (alternative hypothesis). Point estimates and 95% confidence intervals for the response rates will be reported. Alpha (probability of Type I error) for hypothesis tests will be 0.1. If 4 or more of 12 participants in an arm respond (response rate of 33% or greater), the treatment will be considered promising for further investigation. **Efficacy evaluable population:** All participants who receive at least 1 dose of study drug(s) will be evaluated for the primary endpoint. Participants who develop rapid symptomatic disease progression or drop out early due to death will be treated as non-responders. Participants who develop early toxicities that require treatment delay or discontinuation will continue to be evaluable on study. Participants may be replaced in either arm if they complete randomization but do not complete any cycles of therapy. **The toxicity evaluable population**: Participants who have completed at least 1 treatment cycle on either arm will be considered evaluable for toxicity. **Preferable treatment arm will be decided as follows**: • If both arms have comparable response rates, the investigators will perform a comprehensive review of both the response data and toxicity data to decide which study arm is the preferable treatment moving forward.

8.2 Schedule of Assessments

	Baseline/ Screening[a]	Cycle 1[b]	Cycle 2	Cycle 3	Cycle 4	Follow-up Visit 1 and 2[d]	Additional Follow-up Visits[e]	Early Termination Visit[f]
Obtain Informed Consent	X							
Participant History	X							
Inclusion/Exclusion criteria	X							
Biopsy of Target Lesion[c]	X	X						
Prior/concomitant medications	Collected from Screening to Follow-up							
Physical Examination	X	X	X	X	X	X		X
Performance status	X	X	X	X	X	X		X
Height/Weight	X	X	X	X	X	X		X
Vital Signs	X	X	X	X	X	X		X
Complete Blood Count	X	X	X	X	X	X		X
Complete Metabolic Panel, LDH	X	X	X	X	X	X		X
Thyroid function testing[g]	X	X	X	X	X	X		X
Pregnancy test (serum)	X	X	X	X	X	X		X
HCV, HBV, HIV Testing	X							
CT scan[h]	X				X	X		X
MRI Brain	X							
ECG	X							
Adverse Events	Collected from consent to 100 days after drug discontinuation							
Drug Administration		X	X	X	X			
Research blood (~40mL)	X	X	X	X	X	X		X

PD-L1 expression on banked tumor specimen if available	X							
Survival Data						X	X	X

[a]Screening assessments are recommended to be performed within 28 days prior to treatment unless otherwise specified above
[b]Each cycle=21 days±4 days
[c]Biopsy at baseline for all participants within 14 days of Cycle 1, Day 1. On-treatment biopsy must be performed within 14 days±5 days of first dose of study drug.
[d]Follow up period begins when the last dose of study therapy is administered. Follow-up visit 1=21 days from last dose ± 7 days. Follow-up visit 2=42 days from last dose ± 7 days. If the participant completed follow-up visit 1 and follow-up visit 2 and *has* progressed, the participant is not required to have scans every 12 weeks. Survival could be assessed via calls every 3 months (±7 days). If a participant is off treatment and *has not* progressed, they would continue to visit the site and have scans every 12 weeks.
[e]Additional follow-up visits will be scheduled every 3 months ±7 days. For participants who end treatment for toxicity, scans should continue every 12 weeks until progression of disease. After progression of disease, survival calls will occur every 3 months (±7 days).
[f]For participants who terminate the study early, follow-up will begin 21 days from the last dose (follow-up visit 1).
[g]TSH will be checked at every visit and will reflex to check free T4 if abnormal.
[h]Per standard of care to provide data for RECIST measurements as appropriate for each participant per the investigator physician. CT scans will be performed at baseline (-7 days), Week 12, Week 18, and every 12 weeks (±7 days) thereafter until progression of disease, death, or end of study for up to 2 years. A CT scan of the chest, abdomen and pelvis or an MRI of the abdomen and pelvis plus a non-contrast CT of the chest are acceptable.