PARKER INSTITUTE FOR CANCER IMMUNOTHERAPY

Statistical Analysis Plan for

Protocol Number: PICI0025

Protocol Title: An Exploratory Study of Nivolumab with or without Ipilimumab According to the Percentage of Tumoral CD8 Cells in Participants with Advanced Metastatic Cancer

IND Number:	138520
Sponsor:	Parker Institute for Cancer Immunotherapy 1 Letterman Drive Suite D3500 San Francisco, CA 94129
SAP Version Number:	1.0
Date Final:	10 January 2022

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1 TABLE OF CONTENTS

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2 INTRODUCTION

The aim of this study is to provide a prospective classification of CD8 high (immunologically "hot") versus CD8 low (immunologically "cold") tumors at the time of treatment, based on the percentage of CD8 cells in a tumor biopsy, and to address the predictive value of the CD8 biomarker for selecting patients for treatment with nivolumab with or without ipilimumab.

The purpose of this document is to provide details of the planned clinical analyses for PICI0025. The analyses specified in this document supersede the high-level analysis plan described in the protocol. Statistical analyses will be performed consistent with the principles of the ICH Guidance for Industry E9 Statistical Principles for Clinical Trials.

3 STUDY DESIGN

This is an open-label, exploratory study to evaluate nivolumab with or without ipilimumab, with treatment assigned based on the percentage of tumoral CD8 cells at the time of treatment in participants with varying advanced solid tumors.

After consenting to participate in this clinical trial, participants will undergo a tumor biopsy. The tumor tissue will be sent to a Clinical Laboratory Improvement Amendment (CLIA)- and College of American Pathologists (CAP)-certified Immunohistochemistry and Image Analysis Laboratory to determine the percentage of tumoral CD8 cells. Participants will be assigned an immunotherapy regimen according to the percentage of CD8 cells in their tumor biopsies.

There are two distinct cohorts enrolled in this study.

- Advanced Metastatic Cancer: enrolled participants with varying advanced solid tumors.
    - Participants with ≥ 15% CD8 cells in their tumor biopsies (ie, CD8 high tumors) will be treated with nivolumab 360 mg every 3 weeks (Q3W) for 4 cycles, followed by nivolumab maintenance 480 mg every 4 weeks (Q4W). At the time of disease progression, participants may crossover to the CD8 low arm or discontinue treatment.
    - Participants with < 15% CD8 cells in their tumor biopsies (ie, CD8 low tumors) will be treated with nivolumab 360 mg Q3W and ipilimumab 1 mg/kg Q3W for 2 doses and then every 6 weeks (Q6W) for 2 doses, followed by nivolumab maintenance 480 mg Q4W.
- Advanced Prostate Cancer (Protocol Amendment 3): enrolled participants with advanced prostate cancer.
    - Participants with ≥ 15% CD8 cells in their tumor biopsies will be treated with nivolumab 360 mg Q3W for 4 cycles, followed by nivolumab maintenance

480 mg Q4W. At the time of disease progression, participants may crossover to the advanced prostate cohort CD8 low arm of ipilimumab 3 mg/kg and nivolumab 1 mg/kg or discontinue treatment.

- Participants with < 15% CD8 cells in their tumor biopsies (ie, CD8 low tumors) will be randomly allocated into 1 of 2 treatment arms using different doses of ipilimumab.
  - Prostate Cohort A: nivolumab 1 mg/kg Q3W and ipilimumab 3 mg/kg Q6W for 2 cycles, then nivolumab maintenance 480 mg Q4W until disease progression or intolerable toxicity.
  - Prostate Cohort B: nivolumab 1 mg/kg Q3W and ipilimumab 5 mg/kg Q6W for 2 cycles, then nivolumab maintenance 480 mg Q4W until disease progression or intolerable toxicity.

Up to 200 participants with advanced metastatic cancer could be enrolled. A total of 20 participants with advanced prostate cancer and tumoral CD8 < 15% could be enrolled into the Advanced Prostate Cancer portion of the study (10 per treatment arm).

3.1 Protocol Synopsis

The Protocol Synopsis is included in Section 8.1.

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 clinical benefit rate (CBR) of nivolumab with or without ipilimumab in participants with advanced metastatic cancer, including advanced prostate cancer. • To assess the proportion of participants in the nivolumab plus ipilimumab arm whose tumors will change from CD8 low to CD8 high as measured by a change in the percentage of tumoral CD8 cells.	• CBR is the proportion of participants who show clinical benefit, defined as CR, PR, or SD for ≥ 6 months as best response by RECIST v1.1. • Change in the percentage of CD8 cells in on-treatment biopsies from baseline.
Secondary	
• To determine the safety and tolerability of nivolumab with or without ipilimumab in participants with advanced metastatic cancer, including advanced prostate cancer.	• Incidence and severity of AEs based on CTCAE v5.0. • ORR: Defined as CR or PR as best response by RECIST v1.1 assessment.

Objectives	Endpoints
• To determine the ORR of nivolumab with or without ipilimumab in participants with advanced metastatic cancer, including advanced prostate cancer. • To assess the association of percentage of CD8 infiltration in tumor samples with clinical outcomes (ORR, PFS, and OS).	• PFS: Defined as the time from initiation of study therapy to date of first documented progression of disease or date of death due to any cause. • OS: Defined as the time from initiation of study therapy until death due to any cause.
Exploratory	
• To evaluate tumor immune biomarkers and their association with treatment outcomes. • To evaluate changes in prostate-specific antigen (PSA) (advanced prostate cancer). • To assess feasibility of implementing the ApricityCare™ digital application (app) for participants being treated with immune checkpoint inhibitor(s) and the use by study staff of ApricityOncology™ website.	• Clinical responses based on a composite biomarker derived from nucleic acids, epigenetics, protein, immune cell characteristics, or other factors (CD8 and other biomarkers). • Additional biomarkers of primary resistance to nivolumab or ipilimumab combined with nivolumab beyond the percentage of tumoral CD8 cells based on additional immune evaluation of baseline and on-treatment biopsies or blood samples. • Potential relationship of T-cell phenotypic characteristics and immune characteristics in the tumor microenvironment in participants on nivolumab monotherapy and nivolumab in combination with ipilimumab with clinical outcomes (clinical benefit endpoints and AEs with an interest in immune-related AEs). • Within each study intervention arm, explore the potential relationship of clinical response/resistance/AE with: o mRNA quantity and expression in tumor and/or PBMCs o Germline DNA and/or tumor genomics o Multiparameter cytometry of tumor and/or PBMCs o Immune markers in PBMCs o Blood circulating analytes o TCR repertoire in tumor and peripheral blood o Baseline and on-treatment microbiome • Identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or mechanism of

Objectives	Endpoints
	action of nivolumab and/or ipilimumab in combination with nivolumab. • Change in PSA from baseline (advanced prostate cancer). • Frequency of ApricityCare™ app usage by participants and frequency of ApricityOncology website access by study staff.

3.3 Determination of Sample Size

A total of up to approximately 200 participants with varying tumor types will be enrolled. Enrollment to initial biopsy may be about 10% higher (ie, approximately 220 participants) to account for unexpected challenges obtaining CD8 infiltration information. The selection of 200 participants allows minimum reasonable numbers in the CD8 high and CD8 low tumor groups in larger tumor populations to report subgroup response rates, the transformation from CD8 low to high, as well as to predict response from marker and clinical information. Details of the sample size determination can be found in the protocol section 9.1.

3.4 Analysis Timing

Analysis for the Advanced Metastatic Cancer and Advanced Prostate Cancer portions will be performed independently and at different times due to differences in enrollment timelines.

The analysis of complete data for the clinical study report (CSR), described in the main body of this document, will be performed after all participants have been followed for at least 9 months or have discontinued early from the study, and all data from the study through the clinical cutoff date have been entered and reviewed for completeness.

Analysis of efficacy and safety endpoint may be performed prior to the CSR analysis. These results may be presented and/or published prior to the CSR analysis.

The study will formally end once 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.

4 STUDY CONDUCT

4.1 Intervention Assignment

The advanced metastatic cancer portion of this study is not randomized. Treatment assignment will be based on the percentage of tumoral CD8 cells at the initial biopsy. Participants who have a tumor with $\geq$ 15% CD8 cells will receive nivolumab monotherapy, and participants who have a tumor with < 15% CD8 cells will receive ipilimumab in combination with nivolumab.

Approximately 20 advanced prostate cancer participants who have a tumor with < 15% CD8 cells will be randomly allocated to receive nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg (Prostate Cohort A) or nivolumab 1 mg/kg in combination with ipilimumab 5 mg/kg (Prostate Cohort B) in a 1:1 ratio. All advanced prostate cancer participants who have a tumor with ⩾ 15% CD8 cells will receive nivolumab monotherapy. Participants who are randomly allocated but do not receive study intervention for any reason may be replaced. Randomization will be performed by the Sponsor.

Study intervention will be administered by site personnel and tracked using drug accountability records.

4.2 Blinding

This is an open-label trial; therefore, the Sponsor, Investigator, and participant will know the study intervention administered.

4.3 Safety Monitoring for Advanced Metastatic Cancer

The safety of nivolumab and ipilimumab therapies will be monitored during the trial as per the interim analyses described in Section 5.9.

4.4 Safety Monitoring for Advanced Prostate Cancer

As the combination regimen with ipilimumab 5 mg/kg has not been extensively studied, in addition to adverse events being reviewed by the Sponsor on an ongoing basis and investigator meetings convening approximately every 2 weeks to discuss and review safety events, a safety pause is included after the 5th patient has initiated treatment with ipilimumab at the 5 mg/kg dose level.

Enrollment will pause until all participants have been followed for at least 6 weeks. The safety pause will apply to both cohorts to preserve random allocation; however, the safety assessment as follows will apply to the ipilimumab 5 mg/kg cohort specifically. The initial 5 participants enrolled in the ipilimumab 5 mg/kg cohort will be observed for the occurrence of treatment-related adverse events (TRAEs) necessitating discontinuation of both agents from the beginning of treatment through completion of the first cycle (ie, 6 weeks).

If 3 or fewer of the first 5 participants in the ipilimumab 5 mg/kg cohort experience a TRAE leading to discontinuation of both agents, enrollment for that specific cohort will continue as planned until a total of approximately 10 participants are enrolled. If 4 or more of the first 5 participants of the ipilimumab 5 mg/kg cohort experience a TRAE leading to discontinuation of both agents, enrollment into the cohort will be suspended, and an ad hoc safety review (conducted by Investigators and Sponsor representatives) will be performed to assess the available data and provide a recommendation, which may include, but is not limited to, modification or discontinuation of the cohort, and will be documented in the study records. Only TRAEs leading to treatment discontinuation of both agents occurring up until the 5th

participant in each cohort completes Cycle 1 will be included—dose delays for adverse events not otherwise meeting criteria at that time will not be counted. The stopping rule was chosen as this corresponds to a > 80% chance that the toxicity rate in the cohort is > 40%, assuming a beta (0.8, 1.2) prior.

Should the ipilimumab 5 mg/kg cohort demonstrate 6 or greater treatment-related adverse events requiring discontinuation of therapy at any time, enrollment will be suspended until an ad hoc safety review convenes and provides a recommendation, as described above.

5 STATISTICAL ANALYSIS

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, interquartile ranges (IQR; 25th to 75th percentile), minimums, and maximums.

5.1 Populations for Analysis

For purposes of analysis, the following populations are defined (Table 2):

Table 2: Populations for Analysis

Population	Description
Safety Population	All participants who received at least one dose of study drug. Participants will be analyzed according to the study intervention actually received.
Modified Intent-to-Treat (mITT) Population	All participants with sufficient biopsy results to be assigned to a treatment arm and who received at least 1 dose of study drug. Participants will be analyzed according to the study intervention to which they were assigned.
On-treatment Biopsy Population	All participants with at least 1 on-treatment biopsy with sufficient CD8 results will be included in the analyses of changes in CD8 counts.

5.2 Analysis of Study Conduct

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

The participant time on treatment and time on study will be presented in a summary table. Time on treatment is defined as the date from first dose of study intervention until the date of last dose of study intervention. Time on study is defined as the date from first dose of study intervention until the date of death or last contact. The number of participants currently on

treatment and study will presented along with the median time on treatment/study and the associated range. Time on treatment will be calculated using the Kaplan-Meier method, where participants who have discontinued treatment are considered to have an event and participants remaining on treatment are censored at their most recent treatment date. Time on study will be calculated using the reverse Kaplan-Meier method, where participants who remain on study (active treatment or in follow-up) are considered to have an event and participants who died or have discontinued the study are censored at their death or end of study date.

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, cancer location, stage at initial diagnosis, prior lines of systemic cancer therapy, and CD8 percentage at screening.

The baseline value of any variable will be defined as the last value recorded on or before the date of first administration of study intervention.

5.4 Efficacy Analysis

The efficacy analysis will be based on the modified Intent-to-Treat (mITT) Population, which comprises all enrolled participants with sufficient biopsy results to be assigned to a treatment arm and who received at least one dose of study drug, unless otherwise specified. Participants will be analyzed according to the study intervention to which they were assigned.

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 Endpoints

The co-primary endpoint of CBR will be reported among all participants within each study intervention group with a 95% credible interval assuming a beta (0.4, 1.6) prior. CBR is the proportion of participants who show clinical benefit, defined as CR, PR, or SD for $\geqslant 6$ months as best response by RECIST v1.1 (Eisenhauer, 2009). Per RECIST, to be assigned a best overall response of complete response (CR) or partial response (PR), changes in tumor measurements must be confirmed by a repeat assessment that should be performed no less than 4 weeks after the criteria for response are first met. The duration of SD is defined as the time from the date of first dose of study intervention until the date of radiographic disease progression per RECIST. If no radiographic progression has occurred and the most recent tumor assessment with overall response of SD occurred < 6 months after the date of first dose of study intervention, the participant will not have met the SD duration criterion and will not

be considered a CBR responder. Participants who do not have a disease assessment will be counted as not having clinical benefit.

For the second co-primary endpoint, the absolute change in the percentage of CD8 cells in on-treatment biopsies from baseline will be reported with a 95% credible interval with no prior for participants in the on-treatment biopsy population. In addition, the number of participants with baseline percentage of CD8 counts < 15% who "convert" from a cold to hot tumor (any on-treatment biopsy with percentage of CD8 counts ≥ 15%) will be summarized. The proportion of participants who convert from cold to hot will be reported with a 95% credible interval with no prior.

5.4.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include ORR, PFS, and OS and the association between CD8 counts and response.

5.4.2.1 Objective Response Rate

Objective Response Rate (ORR), is defined as the proportion of participants who attain a best overall response of CR or PR, as determined by RECIST version 1.1. Confirmation of response by a repeat tumor assessment is 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).

A 95% credible interval for ORR will be calculated assuming a beta (0.4, 1.6) prior.

5.4.2.2 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the time from initiation of study intervention 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.

5.4.2.3 **Overall Survival**

Overall Survival (OS) is defined as the time from initiation of study intervention 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 5.8.2 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.

5.4.2.4 **Association of CD8 with clinical outcomes**

Several analyses will be performed to investigate the association between the percentage of CD8 cells and clinical outcomes.

- Among the participants who had tumors that converted from cold (CD8 <15%) at baseline to hot (CD8 $\geq$ 15%) at any on-treatment biopsy, the following will be reported:
    - The number and proportion of patients who met ORR response criteria. A 95% credible interval will be estimated with no prior.
    - The number and proportion of patients who met CBR response criteria. A 95% credible interval will be estimated with no prior.
- Logistic regression models will be fit to assess the relationship between percentage of CD8 and clinical response (ORR and CBR). Each regression model will include an intercept term. P-values will be calculated using a Wald test to test whether the coefficient for the CD8 variable is significantly different from 0. See Table 3 for details about each regression model.

Table 3: Logistic Regression Model Parameters

Model number	Response variable (y)	Explanatory variable (x)	Analysis Population
1	CBR	Baseline percentage of CD8 cells	mITT Population
2	ORR	Baseline percentage of CD8 cells	mITT Population
3	CBR	Maximum percentage of CD8 cells across all on-treatment biopsies	On-treatment Biopsy Population
4	ORR	Maximum percentage of CD8 calls across all on-treatment biopsies	On-treatment Biopsy Population
5	CBR	Absolute change between baseline and maximum percentage of CD8 cells across all on-treatment biopsies	On-treatment Biopsy Population
6	ORR	Absolute change between baseline and maximum percentage of CD8 cells across all on-treatment biopsies	On-treatment Biopsy Population
7	CBR	CD8 Conversion Flag (1 = CD8 converter, 0 = non-converter)	On-treatment Biopsy Population
8	ORR	CD8 Conversion Flag (1 = CD8 converter, 0 = non-converter)	On-treatment Biopsy Population

5.4.3 Exploratory Efficacy Endpoints

5.4.3.1 Prostate-specific Antigen Analysis (Advanced Prostate Cancer)

For the Advanced Prostate Cancer participants, descriptive statistics will be used to evaluate PSA at each timepoint. The absolute and percent changes from baseline will be summarized at each timepoint.

5.4.4 Subgroup Analyses

Efficacy endpoints (CBR, ORR, CD8 conversion) may be presented by tumor type if a tumor type has at least 5 participants enrolled in a treatment group.

5.5 Biomarker Analysis

Biomarker exploratory analyses will be determined based on study outcomes and further described in a translational analysis plan.

5.6 Safety Analysis

The safety analysis will be based on the Safety Population, which comprises all participants who receive at least one dose of study drug. Participants will be analyzed according to the study intervention actually received.

Safety and tolerability will be assessed through AEs, clinical laboratory parameters, vital signs, and ECGs.

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) will be summarized by treatment arm using descriptive statistics. The number of skipped doses will also be summarized by treatment arm.

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. A treatment-related adverse event (TRAE) is defined as any TEAE assessed by the Investigator to be 'Possibly', 'Probably', or 'Definitely' related to any study intervention, as well as AEs with missing relationship. An immune-related adverse event (IRAE) is defined as a TRAE that matches a select list of coded preferred terms that have been identified by medical review.

Handling of missing and partial-missing AE dates is described in Section 5.8.1.

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

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

Treatment-emergent and treatment-related AEs will also be summarized by coded preferred Term, system organ class, and severity. In addition, separate summaries will be generated for SAEs.

The following listings will be generated:

- TEAEs
- SAEs
- 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, aspartate aminotransferase, creatinine, platelet count, potassium, sodium, and white blood cells [WBC]) 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 Patient-Reported Outcomes Analysis

For participants enrolled into the Advanced Prostate Cancer cohort, an exploratory analysis may be performed with the patient-reported dataset collected via ApricityCare™, including but not limited to the frequency with which participants complete the daily symptom survey in ApricityCare™, and the frequency of Apricity website access by investigative sites.

5.8 Missing Data

5.8.1 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.

5.8.2 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.

5.9 Interim Analyses

Ongoing monitoring for safety and futility will be implemented based on the method of Thall and colleagues (Thall et al, 1995) separately in the CD8 high and CD8 low tumor groups for advanced metastatic cancer and advanced prostate cancer participants. Monitoring will be ongoing during enrollment in each group, once a participant receives treatment and their first treatment biopsy is performed. Screening and accrual to each group will continue until

sufficient information is available to assess the stopping rules as defined in the protocol Section 9.3.

6 DIFFERENCES COMPARED TO PROTOCOL

The Protocol defines the secondary endpoint exploration of baseline CD8 counts association with CBR and with OS; this was removed from the SAP and will not be analyzed.

7 REFERENCES

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8 APPENDICES

8.1 Protocol Synopsis

Protocol Title:

An Exploratory Study of Nivolumab with or without Ipilimumab According to the Percentage of Tumoral CD8 Cells in Participants with Advanced Metastatic Cancer

Short Title:

Treatment with Nivolumab and Ipilimumab or Nivolumab Alone According to the Percentage of Tumoral CD8 Cells in Advanced Metastatic Cancer

Rationale:

The aim of this study is to provide a prospective classification of CD8 high (immunologically "hot") versus CD8 low (immunologically "cold") tumors at the time of treatment, based on the percentage of CD8 cells in a tumor biopsy, and to address the predictive value of the CD8 biomarker for selecting patients for treatment with nivolumab with or without ipilimumab.

Key Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To determine the clinical benefit rate (CBR) of nivolumab with or without ipilimumab in participants with advanced metastatic cancer, including advanced prostate cancer. • To assess the proportion of participants in the nivolumab plus ipilimumab arm whose tumors will change from CD8 low to CD8 high as measured by a change in the percentage of tumoral CD8 cells.	• CBR is the proportion of participants who show clinical benefit, defined as CR, PR, or SD for $\geqslant$ 6 months as best response by RECIST v1.1. • Change in the percentage of CD8 cells in on-treatment biopsies from baseline.
Secondary	
• To determine the safety and tolerability of nivolumab with or without ipilimumab in participants with advanced metastatic cancer, including advanced prostate cancer. • To determine the ORR of nivolumab with or without ipilimumab in participants	• Incidence and severity of AEs based on CTCAE v5.0. • ORR: Defined as CR or PR as best response by RECIST v1.1 assessment. • PFS: Defined as the time from initiation of study therapy to date of first

Objectives	Endpoints
with advanced metastatic cancer, including advanced prostate cancer. • To assess the association of percentage of CD8 infiltration in tumor samples with clinical outcomes (ORR, PFS, and OS).	documented progression of disease or date of death due to any cause. • OS: Defined as the time from initiation of study therapy until death due to any cause.

AE = adverse event; CBR = clinical benefit rate; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

Overall Design:

This is an open-label, exploratory study to evaluate nivolumab with or without ipilimumab based on percentage of tumoral CD8 cells at the time of treatment in participants with varying advanced solid tumors. Participants who have a tumor with $\geqslant$ 15% CD8 cells (classified as CD8 high) will receive nivolumab monotherapy, and participants who have a tumor with < 15% CD8 cells (classified as CD8 low) will receive ipilimumab in combination with nivolumab.

Number of Participants:

A total of up to approximately 200 participants will be treated. Beginning with Amendment 2, enrollment will be limited to tumor types known to be responsive to immunotherapy, have high prevalence (> 20%) CD8 $\geqslant$ 15% tumors, and/or have been observed in the study to have tumors transition from CD8 low to CD8 high following initiation of immunotherapy. Beginning with Amendment 3, a total of approximately 20 participants with advanced prostate cancer and tumoral CD8 < 15% will be randomly allocated to 1 of 2 cohorts using combinations of ipilimumab and nivolumab. Advanced prostate cancer participants with tumoral CD8 $\geqslant$ 15% will be enrolled in the nivolumab monotherapy arm. Ongoing monitoring for safety and futility will be implemented based on the method of Thall and colleagues (Thall et al, 1995) separately in the CD8 high and CD8 low tumor groups.

Intervention Groups and Duration:

Advanced Metastatic Cancer: Single-agent nivolumab will be administered at 360 mg intravenously (IV) every 3 weeks (Q3W). Participants who continue to show clinical benefit after the first disease assessment will receive nivolumab 480 mg IV every 4 weeks (Q4W) until progressive disease (PD) or intolerable toxicity. At PD, participants will be allowed to crossover to the CD8 low arm of ipilimumab (1 mg/kg) and nivolumab (360 mg).

For nivolumab and ipilimumab combination therapy, nivolumab will be administered at 360 mg IV Q3W, and ipilimumab will be administered at 1 mg/kg IV Q3W for the first 2 doses and then every 6 weeks for the 3rd and 4th doses, followed by nivolumab 480 mg IV Q4W until PD or intolerable toxicity. After receipt of the first dose of ipilimumab, the Investigator may determine (based on clinical symptoms) the number of future doses of ipilimumab the participant will receive, for a maximum of 4 doses. Participants who stop ipilimumab dosing early due to toxicities, may start nivolumab maintenance (ie, 4 doses [12 weeks] of nivolumab following the first dose).

Advanced Prostate Cancer (Amendment 3): Single-agent nivolumab administered at 360 mg intravenously (IV) every 3 weeks (Q3W). Participants who continue to show clinical benefit after the first disease assessment will receive nivolumab 480 mg IV every 4 weeks (Q4W) until progressive disease (PD) or intolerable toxicity. At PD, participants will be allowed to crossover to the advanced prostate cancer CD8 low arm of ipilimumab (3 mg/kg) and nivolumab (1 mg/kg).

For nivolumab and ipilimumab combination therapy, CD8 low arm will be randomly allocated into 1 of 2 cohorts, using different doses of ipilimumab administered in 6-week cycles. Prostate Cohort A will receive nivolumab 1 mg/kg Q3W and ipilimumab 3 mg/kg every 6 weeks (Q6W) for 2 cycles, then nivolumab maintenance 480 mg Q4W until PD or intolerable toxicity. Prostate Cohort B will receive nivolumab 1 mg/kg Q3W and ipilimumab 5 mg/kg Q6W for 2 cycles, then nivolumab maintenance 480 mg Q4W until PD or intolerable toxicity.

Safety and Futility Monitoring:

Monitoring will be ongoing during enrollment in each group to assess the stopping rules as defined in the protocol (see Section 9.3.1). There is no independent Data Safety Monitoring Committee.

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