Regeneron Pharmaceuticals, Inc.
Protocol #: CMP-001-011

A RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROL, PHASE 2/3 STUDY OF FIRST-LINE INTRATUMORAL CMP-001 IN COMBINATION WITH INTRAVENOUS NIVOLUMAB COMPARED TO NIVOLUMAB MONOTHERAPY IN SUBJECTS WITH UNRESECTABLE OR METASTATIC MELANOMA

Statistical Analysis Plan

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The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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I. Introduction

A. Background and Rationale

Melanoma remains the most common cause of skin cancer death in the United States (US), Europe, and Australia. Despite an evolving understanding of the molecular aberrations and clinical factors that impact outcomes as well as improvements in the therapeutic paradigm, including immunotherapy, metastatic melanoma remains essentially incurable in view of the limited efficacy and the toxicity of the currently available agents. Despite the improved outcomes with programmed cell death protein 1 (PD-1) blockade, more than 60% of patients do not respond to single-agent nivolumab or pembrolizumab. Therefore, there remains a critical need for innovative anticancer therapy in this condition.

CMP-001 is a toll-like receptor 9 (TLR9) agonist comprised of [redacted]. The VLP is composed of a capsid protein derived from bacteriophage Qbeta (Qb). G10 is an ODN that contains CpG and also contains poly-G tails that allow it to form G-quadruplexes. Once administered to a patient, an antidrug antibody response to the VLP (anti-Qb antibodies) develops. Antibody-coated [redacted] is taken up by cells through Fc receptors into the endosome. In plasmacytoid dendritic cells (pDCs), antibody-coated [redacted] is taken up via FcgRII into endosomes where the G10 is released and activates TLR91[1].

Several nonclinical and clinical reports support the hypothesis that TLR9 agonism may enhance the antitumor response of melanoma to PD-1 blockade. The ex vivo addition of a PD-1–blocking antibody to CD8+ T cells from melanoma subjects who had been treated with a TLR9 agonist significantly increased the T cell function for cytokine secretion (Fourcade-2014), providing a rationale for the use of the combination of TLR9 agonists and PD-1–blocking antibodies in cancer therapy.

The protocol for Study CMP-001-011 describes the general approach to analysis of data from the study. This analysis plan describes additional details needed to complete such an analysis.

B. Protocol and Amendment History

This Statistical Analysis Plan (SAP) is based on Protocol CMP-001-011 Amendment 1.

Version	Approval Date	Salient Changes, if any*	Description of change and rationale
Protocol	11 September 2020		
Amendment 1	04 February 2021		

* This table notes changes that require accommodation in analysis plan. Further details of all changes in protocol amendments are included in the protocol.

Per Sponsor's decision, site activation and study enrollment were terminated early for any subjects who had not signed informed consent yet, and the trial has been changed to an exploratory Phase 2 study. Additionally, it has been decided that there would not be in-house blinding, hence the sponsor analysis and reporting team would be unblinded to the assignment of subject treatment. Consequently, the SAP will not necessarily be consistent with the protocol. In case of any discrepancies, this SAP will govern the analysis of data from this study.

II. Study Design

A. Design Overview

This is a randomized, open-label, active-control, exploratory Phase 2 study of first-line CMP-001 administered by intratumoral (IT) injection in combination with intravenous (IV) nivolumab versus nivolumab monotherapy in subjects with Stage III or IV unresectable or metastatic melanoma who have not been previously treated with a programmed cell death protein 1 (PD-1) blocking antibody for metastatic disease. Subjects will be randomized in a 1:1 manner to Arm A to receive CMP-001 IT in combination with nivolumab IV or Arm B to receive nivolumab monotherapy according to the Schedule of Assessments (Protocol Table 1) and Protocol Section 5.1.

During the randomization process, treatment groups will be stratified based on: TNM Stage American Joint Committee on Cancer (AJCC) Cancer Staging Manual Eight Edition (M0/M1a/M1b vs. M1c/M1d), and tumor PD-L1 expression (>=5% vs. <5%).

The primary endpoint of ORR per RECIST v1.1 as determined by BICR will be assessed approximately by two disease assessments after the enrollment of the last subject and the end of the study after a maximum duration of 2 years of study treatment. Subjects enrolled may remain in the study and continue to receive study treatment until a reason for treatment discontinuation is reached but no further subjects will be enrolled from 24Jun2022.

Disease assessments by computed tomography (CT) or magnetic resonance imaging (MRI) and other appropriate measures will be performed beginning predose at Week 10 Day 1 (W10D1) (-7 days) and will be repeated every 6 weeks (e.g, W16D1). Responses (CR, PR, iCR, or immune PR [iPR]) will be confirmed by a follow-up disease assessment performed at least 4 weeks after the initial response date. Disease assessments will continue every 6 weeks while the subject is on treatment. Disease assessments will be conducted every 12 weeks for subjects on study after 1 year. All scans will be performed at least 2 weeks after the previous CMP-001 IT injection to prevent injection-related pseudoprogression. Imaging should not be delayed for delays in treatment.

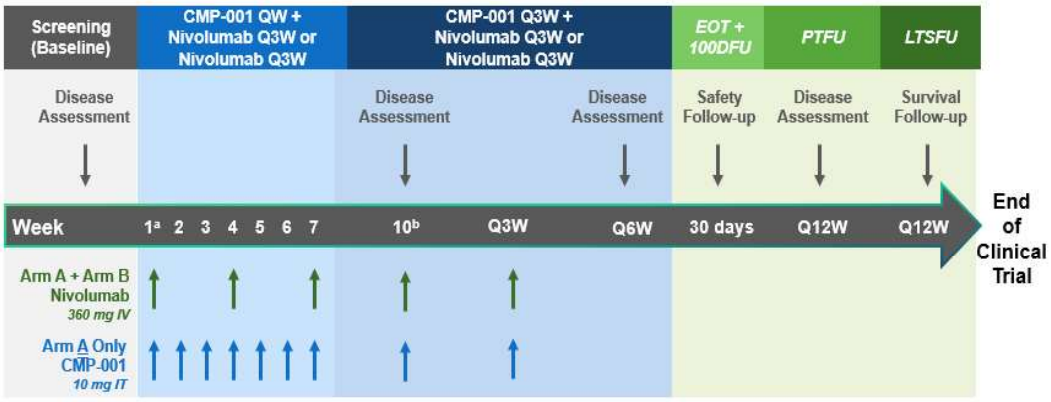
Subjects may continue to receive study treatment beyond progressive disease (PD) according to RECIST v1.1 and will be evaluated by the Investigator according to iRECIST. Subjects with PD per RECIST v1.1 as determined by Investigator assessment should remain on treatment per Investigator discretion and have a follow-up scan performed at least 4 weeks after the initial date of PD to confirm progression per RECIST v1.1.

Subjects who discontinue study treatment should complete an end of treatment (EOT) visit and 100-day safety follow-up contact. Subjects who are posttreatment but have not met criteria for study discontinuation should remain on study for posttreatment follow-up (PTFU) and long-term survival follow-up (LTSFU) and receive study evaluations for efficacy according to the Schedule of Assessments (Protocol Table 1).

At the end of the treatment period (2 years), the Sponsor will not continue to provide supplied study treatment to subjects/investigators unless the Sponsor chooses to extend the study. The Investigator should ensure that the subjects receive appropriate standard of care to treat the condition under study.

The study design is summarized in Figure 1.

Figure 1: CMP-001-011 Study Schema



Note: 100DFU = 100-Day Follow-up; EOT = End of Treatment; LTSFU = Long-Term Survival Follow-up; IT = intratumoral; IV = intravenous; PTFU = Post-treatment Follow-up; Q3W = every 3 weeks; Q6W = every 6 weeks; Q12W = every 12 weeks; QW = weekly; W1D1 = Week 1 Day 1; W10D1 = Week 10 Day 1.
a. The first CMP-001 dose (W1D1) may be administered subcutaneously or by IT injection at the discretion of the Investigator.
b. Disease assessments performed predose beginning at W10D1 (-7 days) and repeated Q6W on treatment and then Q12W for subjects on treatment more than 1 year.

B. Study Population

See Protocol Sections 4.1 and 4.2 for a complete list of the inclusion/exclusion criteria.

C. Sample Size Status

Given the early termination of site activation and study enrollment since 24Jun2022 per Sponsor's decision, the trial has been changed to a Phase 2 study with all the analyses being exploratory. Subjects who have provided written informed consent may complete Screening and be randomized if they meet all eligibility criteria at the discretion of the Sponsor or their representatives. With the enrollment of the last subject on 01Jun2022, the subject status of this study is as follows:

- Screened: 27 subjects
- Screen failure: 7 subjects
- Randomized: 20 subjects
- Treated: 20 subjects

A total of 20 subjects were randomized in a 1:1 ratio to receive either CMP-001 in combination with nivolumab (Arm A) or nivolumab monotherapy (Arm B) with 9 subjects in Arm A and 11 subjects in Arm B as of the early termination of the study enrollment.

D. Treatment Randomization

Subjects who complete Screening procedures and meet inclusion/exclusion criteria will be randomized in a 1:1 ratio to Arm A (CMP-001 in combination with nivolumab) or Arm B (nivolumab monotherapy) using an Interactive Web Response System (IWRS) and stratified by the following factors:

- TNM Stage AJCC Cancer Staging Manual Eighth Edition (M0/M1a/M1b versus M1c/M1d)
- Tumor PD-L1 expression (Tumor Proportion Score, TPS %: ≥ 5% versus < 5%)

During the Screening process, subject-specific values will be recorded for each of the 2 stratification variables. Based on the entered values, the subject will be assigned to a treatment group according to a preprogrammed randomization schedule, which is designed to balance the 2 treatment groups by each variable to the extent possible.

Subjects will be assigned a unique Subject identification (ID) number by the IWRS at randomization. This number will be recorded on the subject's electronic case report from (eCRF) pages and used to identify the subject throughout the study. Once a subject number is assigned, it cannot be reassigned to any other subject.

E. Assessment Schedule

See Protocol Table 1 for the study schedule of assessments.

F. End of Study

As determined by the Sponsor, site activation and enrollment into the study were terminated officially on 24Jun2022 with the trial changed to be a Phase 2 exploratory study. Any subjects meeting the entry criteria and eligible to be dosed in the Screening phase or on active treatment will be allowed to continue on treatment up until the 2-year treatment cutoff per the current protocol.

The end of study is defined as 100 days of safety follow-up after the last dose of the study treatment for the last ongoing subject.

III. Protocol Objectives

Per Sponsor's decision, enrollment was terminated before reaching the sample size planned for the analyses as described in the Protocol. All analyses will be exploratory as a Phase 2 study only. The performance of the statistical analysis for the protocol objectives and endpoints is contingent on the availability of the data source. Detailed information will be provided in the corresponding sections to follow.

A. Primary

<u>Phase 2 Primary Objective</u>

- To determine confirmed objective response rate (ORR) for treatment with first-line CMP-001 in combination with nivolumab versus nivolumab monotherapy in subjects with unresectable or metastatic melanoma

B. Secondary

Phase 2 Secondary Objective

- To evaluate the safety and tolerability of first-line CMP-001 in combination with nivolumab versus nivolumab monotherapy in subjects with unresectable or metastatic melanoma
- To evaluate the efficacy of first-line CMP-001 in combination with nivolumab versus nivolumab monotherapy in subjects with unresectable or metastatic melanoma

C. Exploratory

- [redacted]
- [redacted]

IV. Study Endpoints

A. Primary

Phase 2 Primary Endpoints

- The primary endpoint is the ORR, defined as the proportion of subjects with a confirmed objective response of CR or PR based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) as determined by BICR.

B. Secondary

Phase 2 Secondary Endpoints

- AEs, SAEs, and AEs leading to discontinuation or death and severity of AEs as assessed by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
- PFS, defined as the time from the date of randomization to first date of documented progressive disease based on RECIST v1.1 by BICR or death from any cause, whichever occurs first.
- OS, defined as the time from the date of randomization until death from any cause.
- DOR, defined as the time from date of first documented response (CR or PR) to date of documented progressive disease, based on RECIST v1.1 as determined by BICR

- Disease control rate (DCR), defined as the proportion of subjects who have a confirmed best response of CR or PR, or stable disease (SD) lasting at least 4 months, based on RECIST v1.1 as determined by BICR
- Treatment response in noninjected target lesions based on RECIST v1.1 by Investigator
- Immune objective response rate (iORR), defined as the proportion of subjects with a best overall response (BOR) of immune complete response (iCR) or immune partial response (iPR) based on the immunotherapy Response Evaluation Criteria in Solid Tumors (iRECIST) by Investigator assessment
- Immune duration of response (iDOR), defined as the time from the date of the first immune response (iCR or iPR) to the date of immune confirmed progressive disease (iCPD) based on iRECIST by Investigator assessment
- Immune progression-free survival (iPFS), defined as the time from the date of randomization to date of iCPD based on iRECIST by Investigator assessment or death, whichever occurs first

C. Exploratory

- [redacted]
- Change from baseline in blood concentrations of C-X-C motif chemokine 10 (CXCL10) after treatment with CMP-001
- Baseline, and change from baseline, in tumor or blood measurements of biomarkers related to TLR9

V. Interventions

A. Clinical Trial Material

Nivolumab is a Food and Drug Administration (FDA) approved drug product for the treatment of several types of cancer in multiple regions including the United States (Dec-2014), the European Union (Jun-2015), and Japan (Jul-2014). The physical characteristics of nivolumab are found in the nivolumab Investigator's Brochure.

CMP-001 is an investigational study drug and will be provided by the Sponsor. CMP-001 is provided as a 5 mg/mL solution in a single-use vial. Each single use vial will contain either 1.0 mL extractable volume, for a 5 mg dose of CMP-001, or 2.0 mL extractable volume, for a 10 mg dose of CMP-001. The physical

characteristics and other details about CMP-001 study drug are found in the CMP-001 Investigator's Brochure and the Pharmacy Manual.

At the end of the treatment period, study treatment will no longer be provided to subjects/Investigators unless the Sponsor chooses to extend the study. The Investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

The protocol provides additional product details in Section 6.

VI. General Analytical Considerations

Data analyses will primarily be descriptive and exploratory in nature. Categorical variables will be summarized as the number and percentage of subjects within each category of the parameter (with a category for missing data, if applicable). Continuous variables will be presented as number (n), mean, median, standard deviation, and range (minimum and maximum). Discrete variables will be presented as frequencies or proportions.

Statistical analyses will be performed using SAS® software version 9.4 or higher. MedDRA (version 23.1 or later) will be used for the coding of Medical History and Adverse Events. AEs are graded using Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. World Health Organization Drug Dictionary (WHO-DD) version B3 Global September 2020 (or later) will be used to code the Prior and Concomitant Medications, and Prior Cancer Systemic Treatments.

A. Data Sources

Data are recorded on electronic case report forms (eCRFs). Central laboratory data will be provided via electronic data transfers. Protocol Section 10.2 and Data Management Plan provide additional details regarding data recording and handling. All on-treatment disease assessments will be assessed by a BICR committee using RECIST v1.1 and provided via electronic data transfers.

B. Definition of Baseline

Baseline is defined as the last non-missing observation on or prior to the first administration of study drugs (CMP-001 or Nivolumab), including assessments on Day 1 that are pre-dose. Study Day 1 will be designated as the first day when a subject receives either study drug (i.e., Week 1 Day 1).

C. Missing Data

Unless stated otherwise, missing data will not be replaced with imputed values. When relevant, sections below will address how missing data will be handled for the particular analyses.

Missing or Partial Death Dates

A death date missing the month and day will be imputed as Jan 1st of the year or the day after the date of last known alive, whichever comes later.

A death date missing the day will be imputed as the 1st of the month or the day after the date of last contact, whichever comes later.

Missing Dates in Adverse Events/ Concomitant Medications

Every effort will be made to avoid missing/partial dates in on-study data including AE and medication start and stop dates.

Start dates of AEs/ Concomitant medications will be imputed as follows:

- Completely missing start date will not be imputed.

Start date missing both the month and day will be imputed as:

- The date of the first dose if the year of the start date is the same as the date of first dose.
- Otherwise, Jan 1st of the year of the start date will be used.

Start date missing the day will be imputed as:

- The date of first dose if the year and month of the start date are the same as the date of first dose.
- Otherwise, the 1st day of the month of the start date will be used.

Stop dates of AEs/ Concomitant Medications will be imputed as follows:

- Completely missing stop date will not be imputed.
- Stop date missing both the month and day will be imputed as Dec 31st of the year of stop date.
- Stop date missing the day will be imputed as the last date of the month of the stop date.

After imputation, the imputed date will be compared against the date of death, if available. If the planned imputed date is later than the date of death, the date of death will be used as the imputed date instead.

Missing Dates in Prior Medications

Start or Stop dates of Prior Medications will be imputed as follows:

- Completely missing start or stop date will not be imputed.
- Start or stop date with missing both the month and day will not be imputed.
- Start date missing the day will be imputed as the 1st day of the month of the start date.
- Stop date missing the day will be imputed as the last date of the month of the stop date or the study first dose date, whichever comes earlier.

D. Multiple Study Centers

No adjustment for study center is planned. Data from all investigational sites will be pooled in the analyses.

E. Covariate Adjustment in Primary Analysis

No covariate adjustments are planned.

F. Sample Size Reassessment

Not applicable.

G. Ad-hoc Analysis

There will be an ad-hoc analysis planned with the trigger event being two disease assessments after the enrollment of the last subject. The ad-hoc analysis of the endpoints will follow the efficacy analysis methods described in Section 0 below as well as the safety analysis methods detailed in Section IX below for the exploratory Phase 2 study.

The following unblinded subject information, efficacy-related and safety-related data displays will be produced for the purpose of the ad-hoc analysis. Unless stated otherwise, these displays are summary tables that summarize data by treatment group:

- Subject information
    - Demographics
    - Baseline characteristics
    - Disposition

  - Medical history
  - Cancer history
  - ECOG
- Efficacy
  - ORR, DOR, TTR, PFS per RECIST v1.1 by BICR and Investigator
  - OS
  - Selected subgroup analysis
- Safety
  - Study drug exposure: CMP-001 and nivolumab
  - Prior and concomitant medications
  - Prior and concomitant procedures
  - All TEAEs (SAE, AESI)
  - Summary of clinical laboratory results
  - Summary of ECG results

H. Test Sizes

Given Sponsor's decision to terminate the study enrollment early, any tested hypotheses will be exploratory in essence and tested against 2-sided alternatives, using procedures that provide an expected probability of Type I error (α) of 0.05.

I. Multiplicity

Provided that the study enrollment was terminated early per Sponsor's consideration and the trial has been changed to an exploratory Phase 2 study, the previous sequential gatekeeping strategy is not applicable here anymore, and there will be no control for multiplicity applied. Thus, any tests performed will simply be exploratory and interpreted as such.

J. Analysis Sets

Four analysis populations will be defined for use with various analyses, provided that there are data available for the analysis set to be defined and analysis to be performed. The following table illustrates the relationship between each population and the analyses for which the data from the population will be used.

Analysis Sets	Analysis					
	Baseline	Subject Disposition	Efficacy	Safety	PD	Tumor Biopsy
ITT	X	X	X			
Safety				X		
Per Protocol			X*			
Pharmacodynamic					X	X

* The efficacy analyses will be based on the ITT Analysis Set and may also be performed for the Per-Protocol Analysis Set if deemed appropriate.

1. Intent-To-Treat Analysis Set

The Intent-to-Treat (ITT) Analysis Set is defined as all subjects who are randomized.

2. Safety Analysis Set

The Safety Analysis Set is defined as all subjects who receive at least 1 dose of study treatment.

3. Per-Protocol Analysis Set

The Per-Protocol Analysis Set is defined as all subjects who are randomized and are without important protocol deviations. The list of important protocol deviations will be identified prior to database lock.

4. Pharmacodynamic Analysis Set

The Pharmacodynamic Analysis Set is defined as all subjects who receive at least 1 dose of CMP-001 and have at least 1 measurable sample at Baseline and at least 1 evaluable biomarker sample after CMP-001 administration.

K. Subgroups of Analysis Populations

Not applicable.

L. Data Display Characteristics

Data displays produced for this study will include three types - summary tables, data listings, and figures. Unless stated otherwise, data listings will be produced for all recorded data. Summary tables will be produced as specified in following sections. Additional data listings will be produced for outcome measures that involve extensive procedures to derive the analyzed outcomes, such as efficacy

measures, if appropriate. Figures will be produced when specified in sections to follow.

Data listings will simply list the data recorded on the CRF or derived for each subject. They will be ordered by site, subject number, and date and time of assessment (i.e., visit). When expedient, additional levels of ordering hierarchy may reflect subsets of assessments within subject.

The summary statistics displayed will be a function of the type of data associated with the summarized assessment. Unless stated otherwise in relevant sections to follow, continuous data will be summarized with the number of non-missing values, mean, standard deviation, median, and range (i.e., minimum and maximum). Categorical data will be summarized as the number of subjects within each category, with a category for missing data, if applicable. Percentages of subjects within each of the possible categories will be calculated from the number of subjects in the corresponding analysis population, unless stated otherwise. Some continuous variables may also be grouped into categorical levels and evaluated in frequency tables.

Summary tables will display summary statistics calculated for each of the treatment groups, unless described otherwise in following sections. Tables may have either of two general layouts. When the greatest interest is in direct comparison of one treatment group with the other at particular times, different columns of a summary table will display the statistics for the different treatment groups. The Arm B (nivolumab monotherapy) group statistics will be displayed to the left of Arm A (CMP-001 in combination with nivolumab) group statistics. When the evolution of statistics over time is of greater concern than comparison at particular moments, a group of rows may be designated for the Arm B (nivolumab monotherapy) group; the table columns would be designated for different summary statistics of interest. A subsequent group of rows would then be used for Arm A (CMP-001 in combination with nivolumab) group. In this layout, a group of rows that represent a treatment group would generally be ordered chronologically.

Summary tables, listings and figures will include a “footer” of explanatory notes indicating, at a minimum, the following:

- Program source (e.g., SAS program name)
- Database extraction date (e.g., database lock date or data cut date or data extract date)
- SAS output generation date and time

The purpose of the database extraction date is to link the output to a specific database cut, either active or locked database, that is write-protected for replication

and future reference. Individual data listings will display all the relevant values supporting corresponding tables and figures.

M. Blinded Review of Data

Blinded Independent Central Review will be used for the primary efficacy assessments of tumor response. The BICR charter will be finalized before the first BICR assessment. Blinded Independent Central Review Committee responsibilities include confirmation of disease progression prior to study entry.

This study is being conducted as an open-label study. Per Sponsor's decision, the Sponsor analysis and reporting team will not be blinded to subject treatment assignments or the status of tumor injection.

VII. Subject Accountability

A. Subject Characteristics

Demography. Data collected about the following subject characteristics at the screening visit will be summarized by treatment arm using descriptive statistics for the ITT Analysis Set and listed by subject.

- Age
    - Age will be calculated as the number of years elapsed between birth date and the date of the initial informed consent, adjusted for whether the birthday has passed as of the day of the initial informed consent, which corresponds to the typical calculation of age a person would use in conversation.
- Sex
    - Male
    - Female
        - Childbearing potential
            - Yes
            - No
            - Follicle Stimulating Hormone (FSH) Result
- Race
- Ethnicity

All demography data including informed consent date will be listed.

Baseline Characteristics. Height, Baseline Weight, Baseline Body Mass Index (BMI), ECOG Performance Status at baseline, TNM Stage American Joint Committee on Cancer (AJCC) Cancer Staging Manual Eighth Edition (M0/M1a/M1b versus M1c/M1d) and tumor PD-L1 expression (≥5% versus <5%) will be summarized by treatment arm for ITT Analysis Set and presented in a listing.

Baseline Disease Characteristics. Time since Initial Diagnosis of Primary Cancer to First Dose (Months), Disease Type at Enrollment, PD-L1 Status at Baseline, Tumor Burden at Baseline, Measurable Disease at Baseline, and other key baseline information will be summarized by treatment arm for ITT Analysis Set and presented in a listing.

Melanoma Cancer History. Listings of all collected data related to melanoma cancer history will be provided for ITT Analysis Set. A summary of the following elements and other key information measured at time of diagnosis will also be provided and summarized by treatment arm using descriptive statistics for the ITT Analysis Set:

- Clinical staging at diagnosis
  - Clinical staging
  - Tumor status
  - Nodal status
  - Metastatic disease status
- Pathologic staging at diagnosis
  - Pathologic staging
  - Tumor status
  - Nodal status
  - Metastatic disease status

Melanoma cancer history will be captured on a separate eCRF in the EDC system.

Prior Cancer Treatments. The following variables will be summarized across subjects by treatment arm using descriptive statistics for the ITT Analysis Set to characterize the extent of prior cancer treatments:

- Number of Lines of Prior Systemic Therapies
  - Continuously (mean [SD], median, minimum and maximum)
  - Categorically (0, 1, 2, ≥ 3)
- Most Recent Prior Therapy
  - Prior Systemic Therapy
  - Prior Radiotherapy
  - Prior Cancer-related Surgery
- Any Prior Therapy

  - Prior Systemic Therapy
  - Prior Radiotherapy
  - Prior Cancer-related Surgery
- Reason for Discontinuation from the Most Recent Prior Systemic Therapy
- Reason for Discontinuation from Any Prior Systemic Therapy
- Regimen Best Response on the Most Recent Prior Systemic Therapy
- Regimen Best Response on Any Prior Systemic Therapy
- Administrative Setting of Prior Systemic Therapy
- Time since Completion of Prior Adjuvant Systemic Therapy to Randomization (months)
  - < 6
  - ≥ 6

All prior melanoma treatments will be captured in the EDC separately from other prior medications, where details regarding all prior melanoma treatments, including drug generic name, start date, end date, regimen best response to prior therapy, and administrative setting will be documented in the EDC and listed by subject. Combination treatments should be considered as a single regimen and recorded as such in the EDC. Data on Prior Cancer Radiation and Prior Cancer Surgery will be captured on different pages of eCRF and presented in by-subject data listings.

Medical History Other Than Primary Cancer. At Screening, a general medical history will be obtained, including chronic conditions and comorbidities, relevant acute conditions or infections, surgical procedures unrelated to melanoma, and any reported conditions affecting major body systems during the 10 years prior to Screening. Medical history, to be coded using MedDRA associating lower-level terms with preferred terms and system organ classes by the primary hierarchy, will be summarized by treatment arm in a tabular manner and listed by subject for the ITT Analysis Set. Surgical history will also be presented in a by-subject data listing.

Discrepancies between IWRS and CRF information. Summary tables (i.e., cross-tabulations) by treatment group as randomized across stratification factors will be provided to show any discrepancies between what was reported through IWRS vs. CRF data or clinical database at baseline in the ITT Analysis Set.

- Stage AJCC Cancer Staging Manual Eighth Edition (M0/M1a/M1b versus M1c/M1d)
- Tumor PD-L1 expression ($\geq$5% versus <5%)

B. Disposition

As of the data cutoff date, the number and percentage of subjects who are screen failures, randomized in the study, treated in the study, discontinue study treatment, and discontinue the study will be summarized for all screened subjects. The primary reason for treatment(s) and study discontinuation will be tabulated by treatment arm for the ITT Analysis Set. Subject disposition will also be presented in a by-subject data listing.

Treatment disposition:

- Subjects Completed 2 Years of Treatment
- Subjects Continuing Treatment
- Subjects Discontinued Treatment
    - Adverse Event
    - PD per RECIST v1.1
    - Subject Achieved and Maintained a Confirmed CR or iCR (given subject has been treated with both study treatments for at least 24 weeks, and has received at least 3 doses of both study treatments beyond the date of the initial CR/iCR)
    - Upon Request of the Sponsor or Regulatory Agency
    - Clinical Disease Progression
    - Medically Necessary in the Opinion of the Investigator
    - Subject Withdrew Consent for Treatment
    - Subject Became Pregnant or Began Breastfeeding
    - Subject Lost to Follow-up
    - Death
    - End of Clinical Trial
    - Other

Study disposition:

- Subjects Completed Study
- Subjects Still on Study
- Subjects Permanently Discontinued Study
    - Adverse Event
    - Subject Withdrew Consent
    - Lost to Follow-Up
    - Death
    - Study Terminated by Sponsor
    - End of Clinical Trial
    - Other

Subjects will continue study treatment until they reach a reason for treatment or study discontinuation. Percentages of subjects who withdrew for each of these reasons will be calculated using all members of the relevant analysis set as the denominator. Clinically stable subjects may continue study treatment beyond RECIST v1.1 progression based upon Investigator's judgment of potential benefit until PD is confirmed according to iRECIST. The number and percentage of such subjects continuing to receive study drug beyond RECIST v1.1 progression will be presented.

Study treatment may not continue beyond 2 years from initial dose of study treatment. Subjects who permanently discontinue (for >12 weeks) CMP-001 or nivolumab may not be retreated with the discontinued study treatment in this study. When nivolumab is permanently discontinued due to an immune related AE, CMP-001 must also be permanently discontinued.

Time on Study (TOS) will be summarized descriptively. For subjects who are still on study as of the data cutoff date, TOS will be calculated as follows:

TOS (months) = (Data Cutoff Date – First Dose Date + 1) / 30.4375

As for subjects who exited the study on or prior to the data cutoff date, TOS will be calculated as:

TOS (months) = (Study End Date – First Dose Date + 1) / 30.4375

C. Protocol Deviations and Population Inclusions

All protocol deviations will be captured electronically outside of the Electronic Data Capture (EDC) system in the IQVIA Biotech IL-2 system and presented in the tabular manner and as a by-subject data listing. All deviations will be reviewed on an ongoing basis and classified as major or minor following study review process.

D. Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG Performance Status was measured at Screening and at periodic time points, including the end of treatment, following the initiation of study treatment. At Screening, the ECOG performance status must be either 0 or 1 for the subject to be eligible. The ECOG Performance status is graded according to the ECOG Performance Scale. Shift table analysis of baseline vs. worst and last post-baseline score will be presented. Change from baseline in ECOG Performance Status will be summarized by treatment arm for the ITT Analysis Set. A by-subject data listing will be generated for ECOG data.

VIII. Efficacy Analyses

Efficacy analyses will use data from the ITT Analysis Set or the Per-protocol Analysis Set. Analyses of data from the Per-protocol population may accompany ITT population analyses if deemed appropriate. Disease status will be assessed by computed tomography (CT), or magnetic resonance imaging (MRI) and other appropriate measures beginning pre-dose at W10D1 (-7 days) and will be repeated every 6 weeks (-7 days) (e.g., W16D1, W22D1, etc.).
A response (CR, PR, iCR or iPR [per RECIST v1.1 or iRECIST]) will be confirmed with follow-up disease assessments performed at least 4 weeks after the date of initial response and
all scans should be performed at least 2 weeks after a previous CMP-001 IT injection to prevent injection-related pseudoprogression. Disease assessments will be performed every 12 weeks for subjects continuing on study more than 1 year. Imaging should not be delayed for delays in treatment. All efficacy endpoints will be summarized by treatment arm.

A. Efficacy Endpoints

Confirmed Objective Response Rate (ORR). The primary efficacy endpoint for the study is the confirmed ORR based on RECIST v1.1 as determined by BICR. The confirmed ORR is defined as the proportion of subjects in the analysis set who have a confirmed best overall response (BOR) as CR or PR based on RECIST v1.1 as assessed by BICR. Per RECIST v1.1, CR or PR must be confirmed by a confirmatory assessment performed at least 4 weeks after the initial response. Overall response assessment evaluated after subsequent new anti-cancer therapy will not be considered for ORR calculation.

The confirmed ORR will be calculated as the number of subjects with a confirmed CR or PR divided by the number of subjects in the analysis population [ORR = (confirmed CR + confirmed PR)/number of subjects] in each treatment group for the ITT Analysis Set. 95% exact CIs will be calculated for the ORR using the Clopper-Pearson method for each of the 2 treatment arms. Besides, ORR per RECIST v1.1 by Investigator assessment will also be summarized.

Confirmed Best Overall Response (BOR). The BOR is defined as the best response designation for each subject based on RECIST v1.1 as determined by BICR, recorded between the date of randomization and the date of PD or the date of subsequent new anti-cancer therapy, whichever is earlier. Per RECIST v1.1, CR or PR must be confirmed by a confirmatory assessment performed at least 4 weeks after the initial response. In the case of stable disease (SD), measurements must have met the SD criteria once at least 6 weeks after the date of randomization. The number and percentage of subjects within each BOR category (confirmed CR,

confirmed PR, SD, PD, or not evaluable) will be summarized by treatment arm for the ITT Analysis Set. Besides, BOR per RECIST v1.1 by Investigator assessment will also be summarized.

The best overall response (BOR) will be derived as below:

CR > PR > SD > PD > NE

Subjects who discontinue due to death as a result of disease progression, or disease progression prior to having a post-baseline tumor assessment will be classified as having a best response of PD. Subjects who discontinue prior to having a post-baseline scan for other reasons will be counted as non-responders in the ITT analyses (i.e., these subjects will contribute to the denominator, but not the numerator). Overall response assessment evaluated after subsequent new anti-cancer therapy will not be considered for BOR calculation.

Duration of Response (DOR). Duration of response will be based on RECIST v1.1 as determined by BICR and calculated for confirmed responders in each treatment arm of the ITT Analysis Set. The DOR will be measured from the time at which criteria are first met for CR or PR, whichever is first recorded, until the first date when recurrence or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

DOR is only defined for subjects who have a confirmed BOR of CR or PR. Subjects with an overall response of CR or PR must have a repeated tumor assessment performed no less than 4 weeks after the criteria for response are first met. The first date on which a CR or PR response is noted will be used to calculate DOR, rather than the date of the confirmatory tumor assessment. Subjects who do not have PD or death will be censored at the date of their last disease assessment. Details of the censoring rules are provided in Table 1.

DOR will be calculated as follows:

DOR (months) = (Event/Censoring Date – Response Start Date + 1) / 30.4375

The number and percentage of subjects will be further tabulated according to the response duration of the subject (follow-up time on disease assessment post the initial response of a subject):

- < 6 months
- 6 to < 9 months
- 9 to < 12 months
- 12 to < 18 months
- ≥ 18 months

DOR will be analyzed using the Kaplan-Meier method by treatment arm for the ITT Analysis Set. The median DOR per Kaplan-Meier estimate with two-sided 95% CI calculated using Brookmeyer and Crowley method will be provided. The event-free rate with two-sided 95% CI using Greenwood's formula will be calculated for selected timepoints (i.e., 6 and 12 months). The reasons for censoring will be summarized categorically. A Kaplan-Meier plot of DOR will be generated by treatment arm. Besides, the analysis of DOR based on RECIST v1.1 as determined by Investigator assessment will also be performed.

Progression-Free Survival (PFS). Progression-free survival is defined as the time from date of randomization to the date of documented PD based on RECIST v1.1 as determined by BICR or death from any cause, whichever occurs first. Subjects who are alive and progression-free at the time of analyses will be censored in the analyses. Overall response assessment evaluated after subsequent new anti-cancer therapy will not be considered for PFS calculation.

PFS will be calculated as follows:

PFS (months) = (Event or Censoring Date – Date of Randomization + 1) / 30.4375

All events of RECIST v1.1 disease progression or death will be counted regardless of whether the event occurs while the subject is on study treatment or previously discontinued the study treatment. Subjects who do not experience disease progression or death as of the analysis cutoff date or final database lock will be censored at the date of the last adequate tumor assessment. Date of censoring for these subjects will be based on the last tumor assessment prior to missing the assessments. Censoring rules are summarized in Table 1. If a subject meets the criteria for more than one censoring rule, PFS will be censored at the earliest censoring date. Unless specified otherwise, the analysis methods described for DOR will be used for PFS. Additionally, the analysis of PFS based on RECIST v1.1 as determined by Investigator assessment will also be performed.

Overall Survival (OS). Overall survival will be calculated as the time from the date of randomization to the date of death due to any cause. Subjects who are alive or lost to follow-up as of the analysis cutoff date will be censored at the time of the last study contact date (i.e., date of last known alive). The last contact date will be derived as detailed in Table 2.

Based on these considerations, OS will be calculated as follows:

OS (months) = (Death or Censoring Date – Date of Randomization + 1) / 30.4375

OS will be analyzed using the Kaplan-Meier method by treatment arm of the ITT Analysis Set. A Kaplan-Meier plot of OS will be generated for each treatment arm. The analysis methods described for DOR will be used for OS, unless specified otherwise.

Disease Control Rate (DCR). The confirmed disease control rate is defined as the proportion of subjects in each treatment arm in the analysis set who have a confirmed best response of CR, PR, or stable disease (SD) lasting at least 4 months. Per RECIST v1.1, CR or PR must be confirmed by a confirmatory assessment performed at least 4 weeks after the initial response. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks. Overall response assessment evaluated after subsequent new anti-cancer therapy will not be considered for DCR calculation.

DCR will be analyzed in a similar manner as ORR. Specifically, DCR and the associated 95% Clopper-Pearson CIs will be summarized.

[redacted]

Immune Objective Response Rate (iORR). iORR is defined as the proportion of subjects with an immune best overall response (iBOR) of confirmed immune complete response (iCR) or confirmed immune partial response (iPR) based on immunotherapy Response Evaluation Criteria in Solid Tumors (iRECIST) by Investigator assessment.

Subjects who continue study treatment beyond PD per RECIST v1.1 will be assessed by the Investigator according to iRECIST. Subjects with an iCR or iPR per iRECIST must have a confirmatory assessment performed at least 4 weeks after the initial assessment where response was declared by the Investigator and all scans should be performed at least 2 weeks after the previous CMP-001 IT injection to prevent injection-related pseudoprogression.

The confirmed iORR will be calculated as the number of subjects with a confirmed iCR or iPR divided by the number of subjects in the analysis population [iORR = (confirmed iCR + confirmed iPR)/number of subjects] for each treatment arm of the ITT Analysis Set. The two-sided 95% Clopper-Pearson CIs will be calculated for the iORR.

The immune best overall response (iBOR) will be derived as below:

iCR > iPR > iSD > iCPD > iUPD > NE

If assessments are not performed or cannot be assessed following iUPD, and there is no subsequent iCPD, iSD, iPR or iCR, iUPD will continue to be used and the subject will be censored at the date of iUPD.

Immune Duration of Response (iDOR). iDOR is defined as the time from the date of the first immune response (iCR or iPR) to the date of immune confirmed progressive disease (iCPD) based on iRECIST by Investigator assessment.

iDOR is only defined for subjects who have a confirmed iBOR of iCR or iPR. The first date on which an iCR or iPR response is noted will be used to calculate iDOR, rather than the date of the confirmatory tumor assessment. Subjects who do not develop iCPD or death will be censored at the date of their last disease assessment.

Immune Progression-Free Survival (iPFS). iPFS is defined as the time from the date of randomization to date of iCPD based on iRECIST by Investigator assessment or death from any cause, whichever occurs first.

Table 1: Censoring Rules for the PFS/DOR/iPFS/iDOR

Situation	Outcome	Date	Event Description/ Censoring Reason	PFS/ DOR	iPFS/ iDOR
PD per RECIST v1.1 on/before new anticancer therapy or data cutoff date	Event	Earliest date of tumor assessment documenting PD	PD per RECIST v1.1	X	
Death without PD per RECIST v1.1 and not receiving new anticancer therapy on/before data cutoff date	Event	Date of death	Death without PD per RECIST v1.1	X	
iCPD per iRECIST between scheduled disease assessments on/before new anticancer therapy or data cutoff date, whichever is earlier	Event	Earliest date of tumor assessment documenting iUPD	iCPD per iRECIST		X
Death without iCPD per iRECIST and not receiving new anticancer therapy on/before data cutoff date	Event	Date of death	Death without iCPD per iRECIST		X

Subjects with no post-baseline disease assessments	Censored	First Dose Date	No Adequate Disease Assessment per RECIST v1.1	PFS Only	
No PD per RECIST v1.1 or death as of data cutoff date and subject not received new anticancer therapy or received it after the data cutoff date	Censored	Date of last disease assessment on/before data cutoff date	Alive without Documented PD	X	
No PD per RECIST v1.1 or death as of data cutoff date and new anticancer therapy started before the data cutoff date	Censored	Date of last disease assessment prior to new anticancer therapy	Subsequent Anti-cancer Therapy without Documented PD	X	
PD per RECIST v1.1 or death after new anticancer therapy and the new anticancer started before data cutoff date	Censored	Date of last disease assessment prior to new anticancer therapy	Documented PD or Death after Subsequent Anti-cancer Therapy	X	
PD per RECIST v1.1 or death after new anticancer therapy and the new anticancer started after data cutoff date	Censored	Date of last disease assessment on/before data cutoff date	Documented PD or Death after Subsequent Anti-cancer Therapy	X	
PD per RECIST v1.1 or death immediately following two or more consecutive disease assessments since the last adequate disease assessment	Censored	Date of last adequate tumor assessment prior to the first missed assessment	PD or Death after Missing >= 2 Consecutive Disease Assessments	X	
Discontinuation from study before PD per RECIST v1.1 and death	Censored	Date of last adequate disease assessment	Discontinued from Study without Documented PD or Death	X	
iUPD per iRECIST at the time of PD per RECIST v1.1, continued study treatment without further tumor assessments as of data cutoff date	Censored	Date of the last tumor assessment on/before data cutoff date	No Adequate Disease Assessment per iRECIST		iPFS Only

iUPD per iRECIST, continued study treatment with subsequent disease assessments but no confirmed PD (i.e., iCPD not assigned) or death as of data cutoff date and subject not received new anticancer therapy or received it after the data cutoff date	Censored	Date of the last tumor assessment as of data cutoff date	Alive without Documented iCPD		X
iUPD per iRECIST, continued study treatment, but started a new anti-cancer therapy before data cutoff date without evidence of iCPD or death	Censored	Date of the last tumor assessment prior to new anti-cancer therapy	Subsequent Anti-cancer Therapy without Documented iCPD		X
iCPD per iRECIST or death after new anticancer therapy and the new anticancer started before data cutoff date	Censored	Date of last disease assessment prior to new anticancer therapy	iCPD or Death after Subsequent Anti-cancer Therapy		X
iCPD per iRECIST or death after new anticancer therapy and the new anticancer started after data cutoff date	Censored	Date of last disease assessment on/before data cutoff date	iCPD or Death after Subsequent Anti-cancer Therapy		X
iUPD per iRECIST, continued study treatment, iCPD or death immediately following two or more consecutive disease assessments since the last adequate disease assessment	Censored	Date of last adequate tumor assessment prior to the first missed assessment	iCPD or Death after Missing >= 2 Consecutive Disease Assessments		X
Discontinuation from study before iCPD per iRECIST and death	Censored	Date of last adequate disease assessment	Discontinued from Study without Documented iCPD or Death		X

Situation	**Outcome**	**Date**	**Event Description/ Censoring Reason**	**OS**
Death on/before data cutoff date	Event	Date of death	Death	X

Alive with study completed before data cutoff date	Censored	Study completion date	Alive on or before study completion date	X
Alive or death after data cutoff date with study continuing on/till after data cutoff date	Censored	Data cutoff date	Alive on or before data cutoff date	X
Lost to follow-up prior to data cutoff date	Censored	Last known alive date	Discontinued from study	X
Discontinued study without death and not lost to follow-up on/prior to data cutoff date	Censored	Date of study discontinuation	Discontinued from study	X

Table 2: Last Known Alive Date for the Overall Survival

Source Data	Conditions
Last contact date/last date patient known to be alive from Long-Term Follow-Up eCRF 100-Day Follow-Up eCRF	Use if patient status is reported to be alive. Do not use if patient status is not reported unknown
End of study	Not lost to follow up
Start/end dates from drug administration record	Non-missing dose. Doses of 0 are allowed
Dosing prophylaxis eCRF	Prophylaxis given marked as yes
End of treatment date(s) from the End of Treatment eCRFs	No condition
Tumor assessment (RECIST v1.1 or iRECIST) date	Evaluation is marked as done
Laboratory/PK collection dates	Sample collection marked as done
Vital signs date	At least 1 non-missing parameter value
Physical examination	Evaluation performed marked as yes
12-Lead ECG	Evaluation performed marked as yes
ECOG performance status date	Non-missing ECOG performance status
Start/end dates of adverse events	Non-missing verbatim term
Start/end dates of concomitant medications and procedures	Non-missing verbatim term

B. Primary Efficacy Analysis

Primary Efficacy Endpoint. The primary efficacy endpoint for the exploratory Phase 2 study is the confirmed ORR based on RECIST v1.1 as determined by BICR. ORR and the 95% exact CIs will be calculated using the Clopper-Pearson method for each of the 2 treatment arms in the ITT Analysis Set.

Given Sponsor's decision to terminate the study enrollment early, the previous sample size calculated to achieve the power and effect size desired at the confidence level specified will not be reached. Hence, the analysis will simply be exploratory and interpreted as such.

C. Secondary Efficacy Analyses

The secondary efficacy endpoints include DOR, PFS, OS, DCR, treatment effect in non-injected target lesions based on the RECIST v1.1 by Investigator assessment, iORR, iDOR, and iPFS. Post-progression disease assessments of tumor response based on iRECIST evaluated by Investigator assessment will be summarized in a similar way to the RECIST v1.1 assessment, and will include the calculation of iORR, iDOR, and iPFS by treatment arm using the ITT Analysis Set as described in the previous sections.

iORR: As assessed by Investigator assessment according to iRECIST for the ITT Analysis Set in each of the treatment arm, iORR will be summarized and analyzed in a similar fashion to that of the ORR per RECIST v1.1.

DCR: DCR will be analyzed in a similar manner as ORR. Specifically, DCR and the associated 95% Clopper-Pearson CIs will be summarized.

DOR, PFS, OS, iDOR and iPFS: The secondary endpoints for the exploratory Phase 2 study will be analyzed using the Kaplan-Meier method by treatment arm in the ITT Analysis Set. Median time-to-event with 95% CIs, and event-free rates at 6 and 12 months with 95% CIs will be estimated using Kaplan-Meier methodology. The reasons for censoring will be summarized categorically with the number and percentage of subjects tabulated. Kaplan-Meier plot will also be depicted for visualization.

The following efficacy figures will be generated to display the assessment per RECIST v1.1 by confirmed BICR for each treatment arm of the ITT Analysis set. Additional figures for the Investigator assessment may be produced.

- Swimmer's plot delineating the occurrence of the clinical outcomes of interest over time
    - Duration of treatment
    - Treatment ongoing
    - Time to BOR based on RECIST v1.1 as assessed by BICR, except that PD will be the first occurrence of PD
        - Each BOR category will be displayed in different colors
    - Time to death

- Waterfall plot depicting the best percent change in tumor burden of target lesions from baseline and BOR per RECIST v1.1 by BICR for each subject graphically
    - Tumor burden as reflected by the sum of the diameters (SOD) of all target lesions, concerning the longest diameters for extranodal lesions and short axis for lymph nodes, will be assessed at baseline and at each disease assessment after the first dose of CMP-001
    - Tumor burden change will be calculated as the percentage change in SOD of target lesions from baseline for each efficacy evaluable subject at each disease assessment
    - Each BOR category will be displayed in different colors
- Spider plot presenting the percentage change in tumor burden from baseline for each individual subject over time
    - Each BOR category will be displayed in different colors
- Kaplan-Meier plot displaying time-to-event on DOR, and PFS per RECIST v1.1 by BICR and OS
    - Estimate of median and the corresponding two-sided 95% CIs for median
    - Event-free rates at selected timepoints (i.e., 6 and 12 months)
- Forest plot suggesting ORR and the associated two-sided 95% CIs

Treatment Effect in Non-injected Target Lesions. The treatment effect in non-injected target lesions will be assessed separately from the overall effect. The confirmed ORR in non-injected target lesions based on the RECIST v1.1 Investigator measurements will be summarized for each treatment arm in the ITT Analysis Set using the same approach as that of ORR.

D. Efficacy Analysis on Subgroups of Subjects

The below subgroup analysis (not limited to) for efficacy will be explored using forest plots.

- Age (< 65, ≥ 65)
- Sex (M, F)
- Baseline ECOG PS (0, 1, ≥ 2)
- LDH at Enrollment (Elevated, Normal)
- BRAF mutation (Yes, No)
- Number of Lines of Prior Therapies (1, 2, >=3 [categories can be adjusted based on the data])
- Best Response to Prior Anti-PD-L1 (CR, PR, SD, PD, NE, NA, Unknown)

- Clinical Disease Stage at Enrollment (M0/M1a/M1b, M1c/M1d)
- Tumor PD-L1 Expression (TPS: <5%, >=5%)

F. Other Efficacy Related Analysis

Listings of efficacy-related data will include the following:

- All lesion assessments (target lesion, non-target lesion, new lesion)
- Response assessments
- Time to events

IX. Safety Analyses

The assessment of safety will be based on the following assessments, summarized by treatment arm using data from the Safety Analysis Set. Subjects will be analyzed according to the actual study treatment received.

A. Exposure

The number of CMP-001 and nivolumab doses received by each subject will be summarized descriptively by treatment arm for the Safety Analysis Set. The duration of treatment, dose intensities and relative dose intensity will also be summarized separately as follows with descriptive statistics in a tabular manner and a by-subject data listing.

1. Duration of Treatment (DoT)

Duration of treatment (DoT) of CMP-001 and nivolumab will be summarized in a descriptive manner, respectively. DoT will be calculated as follows:

DoT (months) = [min(last dose date + 21, discontinuation/completion date) – first dose date] / 30.4375

Or

DoT (weeks) = [min(last dose date + 21, discontinuation/completion date) – first dose date] / 7

2. Dosing Intensities

(1) Actual dose intensity (mg/week) will be calculated as the total actual cumulative dose received divided by duration of treatment (weeks) for CMP-001 and nivolumab, respectively.

(2) Planned dose intensity (mg/week) will be calculated as the total planned cumulative dose to be received divided by the planned duration of treatment (weeks) based on the protocol schedule.

Planned Duration of Treatment (weeks) = number of planned treatments * 3 (weeks)

(3) Relative dose intensity (%) will be calculated based on the actual cumulative dose received relative to the planned cumulative dose throughout the duration of treatment as follows:

Relative dose intensity (%) = (actual dose intensity / planned dose intensity) * 100%

3. Dosage Modifications

The number and percentage of subjects with dose delayed, withheld, interrupted, reduced, permanently withdrawn will be tabulated with the reasons for each treatment arm, respectively.

Dosing of CMP-001 and nivolumab, including date and time of each dose, route of administration, dose administered, location of each injection, and the volume injected into each tumor at each dosing visit will be presented in a by-subject data listing per the information from the study drug administration eCRFs.

B. Adverse Events

An AE is an untoward or medical occurrence associated with the use of study drug (active or placebo drug, biologic, or device) in subjects of clinical investigation, which does not necessarily have a causal relationship with the study drug. An AE can therefore be any unfavorable and unintended symptom, sign, disease condition, or test abnormality whether or not considered related to study drug. AEs that do not meet the definition for a Serious Adverse Event (SAE) are considered non-SAEs.

AEs should be recorded upon the first occurrence and followed until resolution. A persistent AE is continuous and does not resolve between Q3W dosing visits. The AE is documented only once unless the grade becomes more severe. If the grade becomes more severe, the AE must be reported again with the new grade.

Specifically, worsening of an ongoing TEAE (i.e., an increase to higher grade) should be recorded as a new AE. Ongoing AEs with a decrease in severity/grade do not need to be captured as new AEs. Any recurrent AE should be reported as new AE each time the AE occurs.

According to Protocol section 8.1.1, disease progression, and associated hospitalizations and deaths, are not considered an AE or SAE in this study.

All other medical occurrences (non-adverse events) that begin before the start of study treatment administration should be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section.

Adverse events starting beyond 100 days after the last dose of the study treatment should not be recorded on the AE eCRF unless they are considered treatment-related SAEs.

Serious adverse events and AEs resulting in discontinuation will be followed until one of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to a baseline value if a baseline value is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- The Investigator and Medical Monitor agree that follow-up is no longer necessary

Adverse event (AE) data are available to the Sponsor from two sources, i.e., the eCRFs and the SAE paper forms and corresponding SAE narratives. While reconciliation will be performed to ensure consistency between the two types of data, the production of data summaries and listings will be based on the data collected on the eCRF.

1. Treatment-emergent adverse event (TEAE)

A TEAE is defined as an AE that started or worsened in severity on or after the date and time (if date is the same) when the study treatment was first administered (W1D1) until 100 days after the last dose of the study treatment or until the initiation of an alternative new anti-cancer treatment, whichever occurs first. For cases in which treatment-emergence could not be ascertained, the event will be classified as treatment-emergent. Pre-treatment AEs are AEs that occur from the time of the informed consent prior to the first dose of study treatment (W1D1).

TEAEs will be coded using MedDRA (version 23.1 or later) and data will be summarized by treatment arm for the Safety Analysis Set. The number and percentage of subjects reporting any TEAEs will be summarized, as well as the number of TEAEs. A subject with more than one TEAEs within the same level of summarization (i.e., system organ class [SOC] or preferred term [PT]) will be counted only once in that level using the highest severity grade and the strongest causal relationship to study drug for the purposes of the incidence tabulations.

AEs are graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. AE summaries may include summaries for all AEs and by the maximum CTCAE grade for the item being summarized (i.e., SOC or PT). In these cases, the outputs will include a column for Any Grades as well as columns for the 5 potential CTCAE grades: Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Life threatening or disabling), or Grade 5 (Death).

If a grade is missing for a TEAE, the event will be counted as grade 3 (Severe) in the TEAE summary tables. If a relationship is missing for a TEAE, the event will be counted as related in the TEAE summary tables.

Related AEs include those which are definitely, probably, and possibly related and those with missing relationship.

A TEAE summary table will be generated including the following:

- Subjects with TEAEs
- Subjects with TEAEs of Grade 3 or higher (Grade 3+)
- Subjects with any treatment-related TEAEs
- Subjects with Grade 3+ treatment-related TEAEs
- Subjects with Serious TEAEs
- Subjects with treatment-related Serious TEAEs
- Subjects with TEAEs of Special Interest
    - Immune-mediated adverse event (IMAEs) based on Investigator's assessment
- Subjects with TEAEs leading to Treatment Discontinuation
- Subjects with TEAEs leading to Death

In addition, the following TEAE summaries tables will be generated. Percentages will be based upon the number of subjects in each treatment arm of the Safety Analysis Set.

- All TEAEs by MedDRA SOC and preferred term
- Grade 3+ TEAEs by MedDRA SOC and preferred term
- TEAEs by MedDRA SOC, preferred term and maximum severity
- Treatment-related TEAEs by MedDRA SOC, preferred term and maximum severity
- TEAEs leading to Death by MedDRA SOC and preferred term
- Serious TEAEs by MedDRA SOC and preferred term
- Treatment-related Serious TEAEs by MedDRA SOC and preferred term
- TEAEs of Special Interest
- TEAEs leading to treatment discontinuation by SOC, PT and NCI CTCAE grading

A by-subject TEAEs data listing, including SOC, preferred term, verbatim term, severity, outcome, relationship to treatment and action taken will be provided.

2. Adverse Events of Special Interest (AESIs)

Immune-mediated Adverse Events (IMAEs). IMAEs are AEs consistent with an immune-mediated mechanism or immune-mediated component for which other etiologies (e.g., infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the subject's eCRF. Every AE must be assessed by the Investigator with regard to whether it is considered immune-mediated. IMAEs will be summarized based on Investigator's assessment as recorded in EDC.

The number and percentage of subjects will be tabulated by the events reported that have the greatest severity and causality. Subjects with multiple severity ratings for a given AE are counted only once under the maximum severity. At each level of subject summarization per unique SOC and preferred term, a subject is counted only once if the subject reported one or more events. Additional AESIs may be added based on the review of the safety data before the final data extract.

C. Deaths

All deaths that occur during the study or within the protocol-specified follow-up period after the last dose of the study drug will be reported. Death information to be included in the summary table concerns the incidence of deaths, along with the primary cause of death by treatment arm for the Safety Analysis Set. All deaths including deaths that occur within 100 days after the last dose of the study treatment or the initiation of an alternative new anti-cancer therapy, whichever is earlier, will be tabulated and presented in a by-subject listing, involving the primary cause of death, duration of treatment and the number of days between the last dose date of the study drug and death.

D. Clinical Laboratory Results

Safety central laboratory data will be summarized by treatment arm and overall using descriptive statistics and presented for each time point for the Safety Analysis Set. Laboratory values reported using a nonnumeric qualifier (e.g., less than [<] or greater than [>] sign), the reported numeric value will be extracted and used for analysis without the qualifier.

1. Incidence of Laboratory Abnormalities

Gradable laboratory values will be evaluated and assigned toxicity grades according to the NCI CTCAE v5.0. Clinically significant post-baseline laboratory values will be reported as AEs. When possible, a diagnosis should be recorded as an AE, rather than the symptoms or isolated laboratory abnormalities related to the diagnosis.

Shift tables will be presented to indicate the number and percentage of patients with directional shifts in CTCAE toxicity grades relative to the baseline, when assessing the worst change (i.e., minimum and/or maximum) in the value of each laboratory test during the treatment period. With regard to laboratory parameters without CTCAE toxicity grades (e.g., serum immunoglobulin), similar shift tables will be constructed per normal range to index the shifts above or below the normal range relative to that of the baseline with the categories of < LLN, WNL and > ULN. WNL and normal will be used when appropriate for urinalysis parameters.

Summary statistics will be provided for gradable parameters with either both directions (e.g., hypocalcemia for the low value of calcium and hypercalcemia for the high value of calcium) or only one of the directions as long as the grading criteria are available per the CTCAE. Subjects will be counted only once for each criterion/direction, but the same subject can be counted for both criteria if the subject has laboratory values that meet each criterion. Subjects who meet the criteria of Grade 1 or higher for the high direction will be classified under Grade 0 for the summarization of the low direction if the CTCAE term for low direction

exists, and vice versa. Change from baseline will be calculated for each parameter of interest when both the baseline and post-baseline values are non-missing.

Additionally, a summary of Hy's Law criteria will be included to indicate if there is any subject potentially meeting Hy's Law criteria during the study for Liver Function Tests (LFTs). The components of the criteria are as follows:

- ALT or AST >= 3xULN (i.e., upper limit of normal)
- Total Bilirubin >= 2xULN
- ALP < 2xULN

Subjects potentially meeting Hy's Law Criteria is defined as those whose ALT or AST >= 3xULN, Total Bilirubin >= 2xULN and ALP < 2xULN at the same visit.

2. Changes in Laboratory Values from Baseline

Hematology and serum chemistry will be summarized in a descriptive manner for the following values that will be derived per unique subject and parameter:

- Baseline value
- Minimum post-baseline value and corresponding change from baseline
- Maximum post-baseline value and corresponding change from baseline
- Last post-baseline value and corresponding change from baseline

The baseline value will be determined using the convention described in Section VI.B. In addition, incidence of the most extreme post-baseline laboratory abnormality from the treatment-emergent period will be summarized for the corresponding parameter. A treatment-emergent laboratory abnormality is defined as a laboratory value whose grade is at least one grade higher than the baseline grade.

By-subject data listings of all central laboratory data will be generated, and all values outside the normal range will be flagged as High or Low. Listings of all clinically significant post-baseline laboratory values from local and central laboratory assessments will be presented in the data listings.

Table 3: Clinical Laboratory Assessments

Hematology	Serum Chemistry	Urinalysis	Other Laboratory Tests

Red blood cells (RBCs) White blood cells (WBCs) Differential WBC count Total leukocyte count, including differential Hemoglobin Hematocrit Platelets	Alanine aminotransferase Albumin Alkaline phosphatase Amylase Aspartate aminotransferase Bilirubin Blood urea nitrogen or serum urea Calcium Chloride Creatinine Glucose Lactate dehydrogenase Lipase Phosphorous Potassium Sodium Total protein	Blood Glucose Nitrites pH Protein Specific gravity WBCs **Microscopic battery:** RBCs, WBCs, epithelial cells, casts (only if significant positive findings on urinalysis)	**Coagulation:** Partial thromboplastin time Prothrombin time International normalized ratio **Thyroid Function Studies:** TSH, T3, free T4 (at Screening) TSH, with reflexive T3 and free T4 if TSH is abnormal (on treatment) **Autoimmune laboratory panel:** Anti-doubled stranded DNA, antinuclear antibody, antineutrophil cytoplasmic antibody, rheumatoid factor, and antibodies to ribonucleoprotein HIV Hepatitis B and C

Abbreviations: RBC = red blood cell; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; WBC = white blood cell.
Note: Refer to the Laboratory Manual for additional information.

E. Vital Signs

The following vital signs were measured at screening and periodic time points (including end of treatment) following the initiation of study treatment:

- Systolic and diastolic blood pressures (mmHg)
- Respiratory Rate (breaths/min)
- Pulse Rate (beats/min)
- Body temperature (Celsius)

Each of these vital signs will be summarized in a descriptive manner for the following values that will be derived per unique subject:

- Baseline value
- Minimum post-baseline value and corresponding change from baseline
- Maximum post-baseline value and corresponding change from baseline
- Last post-baseline value and corresponding change from baseline

The baseline value will be determined using the convention described in Section VI.B. Vital signs will be summarized by treatment arm and overall using descriptive statistics and presented for each time point from baseline to all subsequent post-baseline assessments, including the actual values and change from baseline, for the Safety Analysis Set. Clinically significant post-baseline vital sign findings will be reported as AEs. A by-subject data listing of all vital sign data will be generated.

F. Physical Examination

Detailed information on the physical examinations (height, weight, and BMI) will be listed by subject. Clinically significant post-baseline physical examination findings will be reported as AEs.

G. Prior and Concomitant Medications

All medications administered to the subject from 30 days prior to the first dose of the study drug (W1D1) until 100 days after the last dose of the study treatment (CMP-001 and nivolumab) or until the initiation of an alternative new anti-cancer treatment, whichever occurs first, will be recorded in the EDC. Treatment medications for AEs related to study treatment that occur more than 100 days after the last dose date of the study treatment will also be collected. In addition, at each LTSFU contact, an inquiry will be made regarding the start of any new cancer treatments since the date of the last contact.

Documentation for each medication will include the generic name of the medication, total daily dose, route of administration, date of administration, and indication for use. Combination drugs must be listed separately by each component product and dose. Prior cancer treatment will be recorded separately.

Prior medications. Prior medications are defined as those taken within 30 days prior to the first dose of the study treatment and discontinued before the first dose date of the study treatment.

Concomitant medications. Concomitant medications are defined as medications which are taken at any time prior to 100 days after the last dose of the study treatment (both CMP-001 and nivolumab) or until the initiation of an alternative new anti-cancer treatment, whichever is earlier, and stopped at any time on or after

the first dose date of the study drug. Medications with missing or partially missing start or end dates will be handled according to the conventions described in Section VI.C. If it cannot be determined whether a medication is a prior medication due to partial medication start or end dates, the medication will be considered concomitant. Treatment medications for study-related AEs that occur more than 100 days after the last dose of study drug will be collected.

Medications will be coded using the World Health Organization (WHO) drug dictionary version B3 Global September 2020 (or later) and might be up-versioned by the end of the study. Concomitant medications will be summarized according to the Anatomical Therapeutic Chemical (ATC) class II and preferred term for Safety Analysis Set. The number and percentage of subjects taking concomitant medications will be summarized for each treatment arm in the Safety Analysis Set. Subjects will be counted only once for a given concomitant medication for each ATC class and preferred term in the summary tables. Prior medications will be summarized using the ITT Analysis Set.

Concomitant medications will be presented in a by-subject data listing. The listing will contain the information on both the prior and concomitant medications with an indication on whether the medication is prior or concomitant. The listing will display entries from the Concomitant Medications form, ordered within subject by the Start Date of Medication and listed terms alphabetically.

H. Prior and Concomitant Procedures

All procedures administered to the subject within 30 days prior to the first dose of the study drug (W1D1) until 100 days after the last dose of the study drug (CMP-001 and nivolumab) or until the initiation of an alternative new anti-cancer treatment, whichever occurs first, will be recorded in the EDC.

Prior procedures. Prior procedures are defined as procedures performed within 30 days prior to the first dose of the study drug and discontinued before the first dose date of the study drug.

Concomitant medications. Concomitant procedures are defined as procedures which are performed at any time prior to 100 days after the last dose of the study drug (both CMP-001 and nivolumab) or until the initiation of an alternative new anti-cancer treatment, whichever is earlier, and stopped at any time on or after the first dose date of the study drug.

Concomitant procedures will be presented in a by-subject data listing. The listing will contain the information on both the prior and concomitant procedures with an indication on whether the procedure is prior or concomitant. The listing will

display entries from the Concomitant Procedures form, ordered within subject by the Start Date of Procedure. The listing will also display the recorded terms from the eCRF, adjacent to which, the system organ class and the preferred term will be shown.

I. Electrocardiograms (ECGs)

The 12-lead ECGs were performed at Screening, before the W1D1, W3D1, and W7D1 CMP-001 injections and at end of treatment visit of the study. The following ECG parameters and clinical findings were collected:

- Heart rate (beats/min)
- PR interval (msec)
- QRS interval (msec)
- QT interval (msec)
- QTcF interval (msec)

The mean of the replicate ECG measurements will be calculated and used for the analysis whenever replicates are reported for a subject at a time point. Summaries of actual values and changes from baseline will be presented for each assessment visit. Additionally, each ECG parameter will be summarized in a descriptive manner by treatment arm in the Safety Analysis Set for the following values that are derived per unique subject and ECG parameter:

- Baseline value
- Minimum post-baseline value and corresponding change from baseline
- Maximum post-baseline value and corresponding change from baseline
- Last post-baseline value and corresponding change from baseline

Overall interpretation of ECG parameters (i.e., “Normal”, “Abnormal, Not Clinically Significant” and “Abnormal, Clinically Significant”) at baseline and any applicable post-baseline visit and time point will be summarized categorically with the number and percentage of patients tabulated. Clinically significant post-baseline ECG findings will be reported as AEs.

Categorical analyses of QTcF interval across time points will be performed to display the number and percentage of subjects in a shift from baseline manner with the following thresholds (exclusive categories) to indicate the status of the worst post-baseline value of QTcF (i.e., basically, the maximum post-baseline value) and the status of the last post-baseline value:

- <= 450 msec
- 450 to <= 480 msec
- 480 to <= 500 msec

- > 500 msec

Moreover, the number and percentage of subjects with an increase in QTcF interval from baseline will also be tabulated with the following categories (inclusive levels) to display the status of the maximum post-baseline value of QTcF and the status of the last post-baseline value:

- > 30 msec
- > 60 msec

Detailed information on all ECG data will be depicted by means of a by-subject data listing.

X. Pharmacodynamic Analyses

Concentrations of CXCL10 and other biomarkers will be summarized using descriptive statistics for all time points for the Pharmacodynamic Analysis Set, provided that there are data available for the analysis set to be defined and analysis to be performed.

XI. Exploratory Tumor Biopsy Analyses

Tumor biopsy obtained at Baseline and specified time points during the study may be analyzed for protein, RNA, DNA, or other biomarkers related to TLR9, immune checkpoints, and potential markers of resistance or response to immunotherapy for the Pharmacodynamic Analysis Set, provided that there are data available for the analysis set to be defined and analysis to be performed.

XII. References

1. Lemke-Miltner CD, Blackwell SE, Yin C, Krug AE, Morris AJ, Krieg AM, et al. Antibody opsonization of a TRL9 agonist-containing virus-like particle enhances in situ immunization. J Immunol. 2020 Mar 1;204(5):1386-1394.

2. Goldmacher GV, Khilnani AD, Andtbacka R, Luke RJ, F. Hodi S, et al. Response criteria for intratumoral immunotherapy in solid tumors: itRECIST. Journal of Clinical Oncology.2020;38:15_suppl, 3141.

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Electronic Record and Signature Disclosure: Accepted: 10/11/2022 8:12:54 PM [redacted] Company Name: IQVIA		

Signer Events	Signature	Timestamp
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Electronic Record and Signature Disclosure: Accepted: 10/12/2022 12:20:20 PM [redacted] Company Name: IQVIA		
[redacted] [redacted] Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 10/11/2022 12:21:01 PM Viewed: 10/11/2022 12:24:16 PM Signed: 10/11/2022 12:34:30 PM
Electronic Record and Signature Disclosure: Accepted: 9/29/2022 10:01:59 AM ID: [redacted] Company Name: IQVIA		
[redacted] [redacted] Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 10/11/2022 12:21:00 PM Viewed: 10/11/2022 12:22:24 PM Signed: 10/11/2022 12:23:49 PM
Electronic Record and Signature Disclosure: Accepted: 2/14/2022 6:28:48 PM [redacted] Company Name: IQVIA		

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Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

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Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	10/11/2022 12:21:02 PM
Certified Delivered	Security Checked	10/11/2022 12:22:24 PM
Signing Complete	Security Checked	10/11/2022 12:23:49 PM
Completed	Security Checked	10/19/2022 8:57:07 AM

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