Regeneron Pharmaceuticals, Inc.
Protocol #: CMP-001-010

A MULTICENTER, OPEN-LABEL, PHASE 2 STUDY OF INTRATUMORAL CMP-001 IN COMBINATION WITH INTRAVENOUS NIVOLUMAB IN SUBJECTS WITH REFRACTORY UNRESECTABLE OR METASTATIC MELANOMA

Amendment 2 (Version 3.0) 26 August 2021

Statistical Analysis Plan

Version 1.0
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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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CONTENTS

Abbreviations

Abbreviation	Term
AEs	Adverse Events
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BOR	Best Overall Response
CTCAE	Common Terminology Criteria for Adverse Events
CR	Complete Response
DOR	Duration of Overall Response
ECG	Electrocardiogram
EDC	Electronic Data Capture system
eCRFs	Electronic Case Report Forms
ITT	Intent to Treat
iCR	immune complete response
iCPD	immune confirmed progressive disease
iDOR	immune Duration of Response
iORR	immune Objective Response Rate
iPR	immune partial response
iPFS	Immune Progression-Free Survival
iRECIST	immunotherapy Response Evaluation Criteria in Solid Tumors
MedDRA	Medical Dictionary for Regulatory Activities
ORR	Objective Response Rate
PD	Progressive Disease
PFS	Progression-free Survival
PR	Partial Response
QTcF	QT corrected according to Fridericia
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Stable Disease
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
WHO-DD	World Health Organization Drug Dictionary

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 QbG10, a virus-like particle (VLP) that encapsulates G10, a cytosine linked to a guanine by a phosphate bond (CpG) oligodeoxynucleotide (ODN). 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 QbG10 is taken up by cells through Fc receptors into the endosome. In plasmacytoid dendritic cells (pDCs), antibody-coated QbG10 is taken up via FcgRII into endosomes where the G10 is released and activates TLR9[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 an anti-PD-1 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 anti-PD-1 antibodies in cancer therapy.

The protocol for Study CMP-001-010 describes the general approach to analysis of data from the study. This analysis plan describes additional details needed to complete such an analysis which will be conducted for the clinical study report (CSR).

B. Protocol and Amendment History

This Statistical Analysis Plan (SAP) is based on initial version of Protocol CMP-001-010.

Version	Approval Date	Salient Changes, if any*	Description of change and rationale
Initial	31 August 2020		
Amendment 1	04 February 2021		
Amendment 2	26 August 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 stopped earlier for any subjects who had not signed informed consent yet, and analyses were made exploratory. 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 multicenter, open-label, exploratory Phase 2 clinical study of CMP-001 IT in combination with Nivolumab IV in subjects with unresectable or metastatic melanoma refractory to PD-1 blockade. Eligible subjects must have confirmed disease progression during or within 12 weeks of their last dose of therapy containing a PD-1 blocking antibody for the treatment of unresectable cutaneous melanoma prior to enrollment. All subjects will receive CMP-001 IT and Nivolumab IV according to the Schedule of Assessments (Protocol Table 1) until a reason for treatment discontinuation is reached.

CMP-001 10 mg IT will be administered weekly for 7 doses, after which it will be administered Q3W until the subject meets a condition for discontinuation of study treatment. The treatment will be given for a maximum of 2 years from the start of the study treatment. The first dose of CMP-001 may be administered SC or by IT injection, at the discretion of the Investigator; all subsequent doses are planned to be administered IT. The initial 7 CMP-001 doses on a weekly schedule must be completed before moving on to the Q3W CMP-001 dosing schedule.

If all injectable tumors regress, CMP-001 may be injected SC in the region of prior tumors or draining lymph node bed, at the Investigator's discretion (see Protocol Appendix F). On visits where both study treatments are administered, CMP-001 IT should be administered before Nivolumab. CMP-001 should be administered

until a reason for treatment discontinuation is reached, or for a maximum of 2 years from the start of the study treatment. See Protocol Section 5.1.3. for treatment modifications for CMP-001.

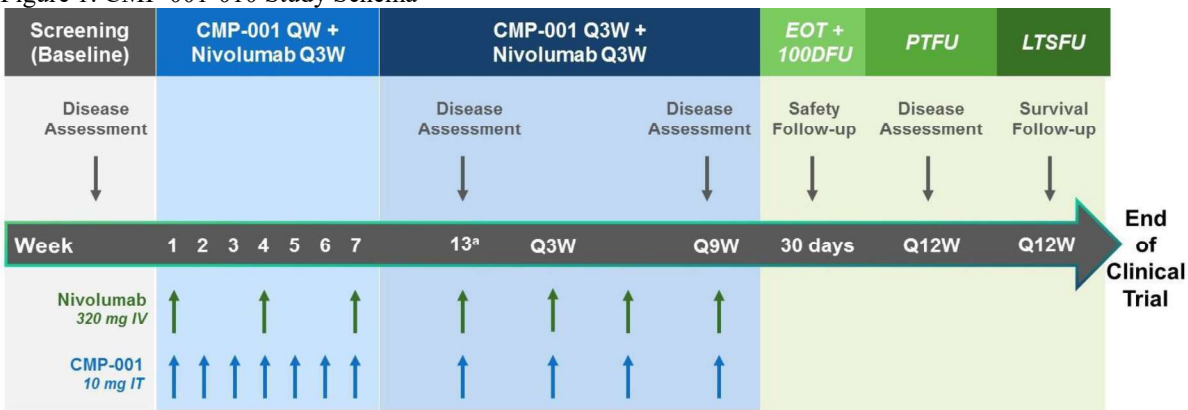
Objective responses will be assessed by BICR and Investigator assessment according to RECIST v1.1. Subjects who continue study treatment beyond PD according to RECIST v1.1 at the discretion of the Investigator will be evaluated by the Investigator according to iRECIST.

Disease status will be assessed by computed tomography (CT) or magnetic resonance imaging (MRI) and other appropriate measures beginning predose at Week 13 Day 1 (W13D1) and repeated every 9 weeks (eg, W22D1) while the subject is on treatment. All scans should 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. Disease assessments may continue every 12 weeks for subjects with a response lasting more than 1 year.

Responses (CR, PR, immune complete response [iCR], or immune partial response [iPR]) will be confirmed by a follow-up disease assessment performed at least 4 weeks after the initial response date, and at least 2 weeks after the last CMP-001 injection.

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

Figure 1: CMP-001-010 Study Schema



Note: 100DFU = 100-Day Follow-up; EOT = End of Treatment; IT = intratumoral; IV = intravenous; LTSFU = long-term survival follow-up; PTFU = posttreatment follow-up; Q3W = every 3 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; QW = every week.

a. Disease assessments performed predose beginning at W13D1 (- 7 days).

B. Study Population

See Protocol Section 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, all the analyses will be descriptive and exploratory. This study has enrolled 44 subjects. A subject is enrolled in the study when they have received the first dose (partial or complete) of study treatment. Subjects who have provided written informed consent may be allowed to complete Screening and enter study treatment if they meet all eligibility criteria, at the discretion of the Sponsor or their representatives.

With the enrollment of the last subject on 30Jun2022, the subject status of this study is as follows:

- 67 subjects were screened
- 23 subjects were screen failures
- 44 subjects started the treatment

D. Treatment Randomization

No randomization will be performed in this study.

E. Assessment Schedule

See Protocol Table 1 for the study schedule of assessments.

F. End of Study

Per Sponsor's decision, site activation and study enrollment were terminated officially on 24Jun2022. All subjects previously enrolled in the study may continue receiving up to 2 years of study treatment per the current protocol.

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

III. Interventions

A. Clinical Trial Material

Nivolumab is an FDA approved drug product for the treatment of several types of cancer in multiple regions including the US (Dec-2014), the EU (Jun-2015), and Japan (Jul-2014). The physical characteristics of Nivolumab are found in the OPDIVO® (Nivolumab) Prescribing Information. Nivolumab will be provided by the sponsor.

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. The physical characteristics and other details about the CMP-001 study drug are found in the IB 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.

IV. Protocol Objectives

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

A. Primary

The protocol lists the following primary objective:

- To determine confirmed objective response with CMP-001 in combination with Nivolumab in subjects with refractory unresectable or metastatic melanoma.

B. Secondary

The protocol lists the following secondary objective:

- To evaluate the safety and tolerability of CMP-001 administered by intratumoral (IT) injection in combination with Nivolumab in subjects with refractory unresectable or metastatic melanoma.

- To evaluate the efficacy of CMP-001 in combination with Nivolumab in subjects with refractory unresectable or metastatic melanoma.
- To assess the pharmacokinetic (PK) profile of CMP-001 in combination with Nivolumab in subjects with refractory unresectable or metastatic melanoma.
- To assess and describe the immunogenicity of CMP-001 in combination with Nivolumab in subjects with refractory unresectable or metastatic melanoma.

C. Exploratory

The protocol (Section 2.1.3) lists the following exploratory objective:

- Evaluate the effect of CMP-001 in combination with Nivolumab on injected and non-injected target lesions in subjects with unresectable or metastatic melanoma.
- Evaluate the pharmacodynamic effects of CMP-001 administered in combination with Nivolumab.

V. Study Endpoints

A. Primary

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 Blinded Independent Central Review (BICR).

B. Secondary

The protocol describes as secondary endpoints the following:

- AEs, serious adverse events (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 version 5.0 (CTCAE v5.0)
- Duration of response (DOR), defined as the time from date of first documented response (CR or PR) to date of documented PD, based on RECIST v1.1 by BICR
- Treatment response in non-injected target lesions based on RECIST v1.1 by BICR
- Progression-free survival (PFS), defined as the time from date of first dose of study treatment to date of documented PD based on RECIST v1.1 by BICR or death, whichever occurs first

- Overall survival, defined as the time from date of first dose of study treatment to date of death
- ORR, DOR, and PFS based on RECIST v1.1 and immune objective response rate, immune duration of response (iDOR), and immune progression-free survival (iPFS) based on immunotherapy Response Evaluation Criteria in Solid Tumors (iRECIST) by Investigator assessment
- Blood concentrations of CMP-001 or its metabolites
- Development of anti-Qb antibodies

C. Exploratory

In addition to the endpoints described above, the following endpoints will be evaluated:

- Response in injected and non-injected target lesions per intra-tumoral Response Evaluation Criteria in Solid Tumors (itRECIST) by Investigator assessment
- Baseline, and change from Baseline, in tumor or blood measurements of biomarkers related to TLR9, immune checkpoints, and potential markers of resistance or response to immunotherapy
- Change from Baseline in blood concentrations of CXCL10 (interferon gamma-induced protein 10) after treatment with CMP-001

VI. General Analytical Considerations

Data analyses will be primarily descriptive and exploratory. 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.

A. Data Sources

Data are recorded on electronic case report forms (eCRFs). Central laboratory data will be provided via electronic data transfers. Protocol Section 11 and the study Data Management Plan provide additional details regarding data recording and handling.

B. Definition of Baseline and Study Day

Baseline is defined as the last non-missing observation prior to the first administration of study drugs (CMP-001 or Nivolumab). Study Day 1 will be designated as the first day a patient 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 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 date after the date of last contact, whichever comes last.

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 last.

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 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. If there is no date of death in the EDC for a subject and the planned imputed date is later than the End-of-Treatment (the last drug received) date + 100 days, then the End-of-Treatment (the last drug received) date + 100 days will be used for the stop date.

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 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.

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 VIII below as well as the safety analysis methods detailed in Section IX below for the exploratory Phase 2 study.

The following 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 for the corresponding analysis set:

- 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

Not Applicable.

I. Multiple Comparisons

No control for the effect of multiple comparisons is planned.

J. Analysis Sets

Five analysis sets 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 Set	Analysis						
	Baseline	Subject Disposition	Efficacy	Safety	PD	Immuno genicity	Tumor Biopsy
Intent-to-Treat	X	X	X				
Safety				X			
Per Protocol			X*				
Pharmacodynamic					X		X
Immunogenicity						X	

* The efficacy analyses 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 receive at least 1 (partial or full) dose of study treatment.

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 receive at least 1 dose of study treatment and are without major protocol deviations.

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.

5. Immunogenicity Analysis Set

The Immunogenicity Analysis Set is defined as all subjects who receive at least 1 dose of CMP-001 and have at least 1 non-missing ADA result 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 subjects. 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. 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 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, minimum, median, 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, listings and figures will include a "footer" of explanatory notes that will indicate, 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 relative values supporting corresponding table and figures.

M. Blinded Review of Data

Blinded Independent Central Review (BICR) RECIST v1.1 assessment will be used for the primary efficacy assessments of tumor response. A detailed charter for the BICR will be created prior to the first BICR assessment.

Blinded Independent Central Review responsibilities also include confirmation of disease progression prior to study entry, in addition to the primary efficacy assessment of the study.

VII. Subject Accountability

A. Subject Characteristics

Demography and Baseline Characteristics. Data collected about the following subject characteristics at the screening visit will be summarized:

- Age
  - Age will be calculated as the number of years elapsed between birth date and the date of the ICF date, adjusted for whether the birthday has passed as of the day of the screening visit. (This corresponds to the typical calculation of age a person would use in conversation.)
- Sex
  - Childbearing potential yes/no
  - Non-childbearing potential, and confirmation by site
- Race
- Ethnicity
- Height
- Baseline Weight
- Baseline Body Mass Index

All demography data including informed consent date will be listed.

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

Medical History Other Than Melanoma Cancer. Medical history including CNS screening will be summarized in a table and listed by subject. Medical history will be coded using MedDRA, associating lower-level terms with preferred terms and system organ classes by the primary hierarchy.

Melanoma Cancer History. Listings of all collected data related to Melanoma history will be provided for ITT Analysis Set. A summary of the following elements will also be provided:

- PD-L1 status

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

Prior Primary Cancer Treatments. Listings of key data related to prior melanoma treatments will be provided for ITT Analysis Set, and include the following information:

- Number of Lines of Prior Systemic Therapies: summarized categorically (1, 2, ≥ 3)
- Any Prior Therapy
  - Prior Systemic Therapy
  - Prior Radiotherapy
  - Prior Cancer-related Surgery
- Reason for Discontinuation from Any Prior Systemic Therapy
- Regimen Best Response on Any Prior Systemic Therapy
- Duration of Exposure to Any Prior Systemic Therapy (months), summarized continuously
- Administrative Setting of Prior Systemic Therapy
- Time since Completion of Prior Adjuvant Systemic Therapy to First Dose Date (< 6 months; ≥ 6 months)

All prior melanoma treatments will be captured in the EDC separately from other prior medications. Combination treatments should be considered as a single regimen and recorded as such in the EDC. Details regarding all prior melanoma treatments, including drug generic name, start date, end date, regimen best response to prior therapy, and administrative setting, as well as key data related to prior melanoma treatments, will be listed by subject for ITT Analysis Set.

Data on Prior Cancer Radiation and Prior Cancer Surgery will be captured on different pages of eCRF and presented in separate by-subject data listings.

B. Disposition

As of the data cutoff date, the number and percentage of subjects who screen fail and enroll in the study (receive at least one dose of study treatment), discontinue study treatment, and discontinue the study will be summarized. The primary reason for treatment(s) and study discontinuation and follow-up status will also be summarized for the ITT Analysis Set.

Study treatment (CMP-001 only or both CMP-001 and Nivolumab) may be discontinued for any of the following occurrences:

- Adverse Event
- PD per RECIST v1.1
- Subject Achieved and Maintained a Confirmed CR or iCR (and has been treated for at least 48 weeks, and has received at least 3 doses of both study treatments beyond the date of 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
- Subject Completed 2 Years of Study Treatment
- End of Clinical Trial
- Other

Study Participation may be discontinued for any of the following occurrences:

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

Percentages of subjects who withdrew for each of these reasons will be calculated using all members of the relevant analysis set for the denominator.

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

Subject disposition will be presented in a by-subject data listing.

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 a by-subject data listing. All deviations will be reviewed on an ongoing basis and classified as major or minor.

VIII. Efficacy Analyses

The primary efficacy analyses will use data from the ITT population. Analyses of data from the Per-protocol population may accompany ITT population analyses if substantial number of ITT population subjects are excluded from the Per-protocol population.

A. Efficacy Endpoints

Confirmed Objective Response Rate (ORR)

The confirmed ORR is defined as the proportion of subjects in the analysis set who have confirmed best response as CR or PR per RECIST v1.1 as assessed by BICR.

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] for the ITT Analysis Set. 95% Clopper-Pearson CIs for the ORR will be calculated.

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. Objective Response assessment evaluated after new anti-cancer treatment will not be considered for BOR calculation.

Confirmed Best Overall Response (BOR)

The Best Overall Response for a subject is the best response designation as assessed by BICR, recorded between the date of the first dose of study treatment and the date of objectively documented progression per RECIST v1.1, or the date of treatment discontinuation, whichever occurs first.

Per RECIST v1.1, CR or PR must be confirmed by a confirmatory response assessment performed at least 4 weeks after the initial response. Objective Response assessment evaluated after new anti-cancer treatment will not be considered for BOR calculation.

BOR will be derived as below:

CR > PR > SD > PD > NE

Disease Control Rate (DCR)

The confirmed disease control rate is defined as the proportion of subjects in the analysis set who have a confirmed Best Overall Response of CR, PR, or stable disease (SD) per RECIST v1.1 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. 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. OR assessment evaluated after new anti-cancer treatment will not be considered for DCR calculation.

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 per BICR measurements will be derived using the same approach as ORR.

Data for the injected target and non-injected target lesions will be analyzed as a secondary efficacy analysis using the following definitions (Goldmacher, 2020).

1. *Injected Target Lesions*

The baseline for each individual injected target lesion is defined as the measurement prior to the first injection of that lesion. Specifically:

- For target lesions injected at W1D1, the baseline is defined as the measurement obtained prior to W1D1.
- For the injection of other accessible non-injected lesions when an injected tumor is clearly decreasing in size, the baseline measurement for these newly injected lesions is defined as the preceding measurement obtained

prior to the initial injection of these lesions and the baseline for these lesions will not be the measurement prior to W1D1.

- Baseline SOD is defined as the sum of diameters of the individual lesion at its respective baseline; thus, if a lesion is not injected until post W1D1, then the baseline for the injected SOD will take the data from different time points into consideration.
- Best change in tumor burden (i.e., maximal percentage reduction in SOD) will also incorporate measurement data from different time points, regardless of whether a lesion was injected after W1D1. However, only measurements taken after the initial injection can be considered for best response.

2. Non-injected Target Lesions

- As long as the non-injected target lesions remain non-injected, the SOD for the non-injected target lesions will be compared against the measurement obtained prior to W1D1.
- If any non-injected target lesions are decided to be injected, then the maximal non-injected effect has been achieved and any subsequent non-injected response is considered non-evaluable.

The injection status of a target lesion will be determined based on the response to the Type of Injection question of the CMP-001 Dosing page. If 'Intratumoral (IT)' is selected at a specific time point, then the lesion is considered injected from that time point onwards and deemed non-injected prior to that injection time point. Once injected, the lesion will be considered an injected target lesion for all subsequent time points, even if not injected later on.

Duration of Response (DOR)

Duration of response will be based on RECIST v1.1 as determined by BICR and calculated for confirmed responders 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 that 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. Per the BOR definition, subjects with an overall response of CR or PR must have a repeat tumor assessment performed no less than 4 weeks after the criteria for response are first met. The first date at which a CR or PR response was noted will be used to calculate DOR, not 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. For subjects who started a subsequent anti-cancer therapy before having a documented PD, the last disease assessment prior to the start of the

subsequent therapy will be used. Details of the censoring rules are provided in Table 1a.

DOR will be calculated as follows:
DOR (months) = (Event/Censoring Date – Response Start Date + 1) / 30.4375

Progression-Free Survival (PFS)

Progression-free survival is defined as the time from first dose of study treatment to the date of documented PD based on RECIST v1.1 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 at the date of their last disease assessment. For subjects who started a subsequent anti-cancer therapy before having a documented PD, the overall response assessment evaluated after new anti-cancer treatment will not be considered for PFS calculation, and the last disease assessment prior to the start of the subsequent therapy will be used. Details of the censoring rules are provided in Table 1a.

PFS will be calculated as follows:
PFS (months) = (Event or Censoring Date – First Dose Date + 1) / 30.4375

All events of RECIST v1.1 disease progression or death will be counted regardless of whether the event occurred while the subject was on study drug or had previously discontinued treatment. Subjects who do not experience disease progression or death before the analysis cutoff date will be censored at the date of 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 1a. If a subject meets the criteria for more than 1 censoring rule, PFS will be censored at the earliest censoring date.

Secondary Efficacy Assessments by Investigator

The secondary efficacy endpoints of ORR, BOR, DCR, DOR and PFS by investigator assessments will be derived using the same approach as above.

Overall Survival (OS)

Overall survival will be calculated as the time from first dose of study treatment to the date of death due to any cause. Subjects who are alive or lost to follow-up at the time of the analysis data cutoff will be censored at the time of last known alive date, or at data cutoff date, whichever occurs first. Censoring rules are detailed in Table 1c, and the last contact date will be derived as shown in Table 2.

OS will be calculated as follows:
OS (months) = (Death or Censoring Date – First Dose Date + 1) / 30.4375

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]. 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 be continue 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) by Investigator assessment.

iDOR is only defined for Subjects who have a confirmed iBOR of iCR or iPR. Subjects with a response of iCR or iPR must have a repeat tumor assessment performed no less than 4 weeks after the criteria for response are first met. The first date at which an iCR or iPR response was noted will be used to calculate iDOR, not the date of the confirmatory tumor assessment. Subjects who did not have iCPD or death will be censored at the date of their last disease assessment. Censoring rules are detailed in Table 1b.

Immune Progression-Free Survival (iPFS).

iPFS is defined as the time from date of first dose of study drug to date of iCPD per iRECIST as assessed by Investigator or death, whichever occurs first. Censoring rules are detailed in Table 1b.

Table 1a: Censoring Rules for the PFS/DOR

Situation	Outcome	Date	Event Description/ Censoring Reason
PD per RECIST v1.1 on/before new anticancer therapy or data cutoff date, whichever is earlier	Event	Earliest date of tumor assessment documenting PD	PD per RECIST v1.1
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
[PFS only] Subjects with no post-baseline assessments	Censored	Date of First Dose of Study Drug	No Adequate Disease Assessment per RECIST v1.1
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
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
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
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
PD per RECIST v1.1 or Death immediately following two or more consecutive disease assessments missed since the last adequate disease assessment	Censored	Date of last adequate tumor assessment prior to missing assessments	PD or Death after Missing >= 2 Consecutive Disease Assessments
Withdrew consent or lost to follow-up before PD per RECIST v1.1 or Death	Censored	Date of last adequate disease assessment	Discontinued from Study without Documented PD or Death

Table 1b: Censoring Rules for the iPFS/iDOR

Situation	Outcome	Date	Event Description/ Censoring Reason
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
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
[iPFS only] 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
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
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
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
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
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
Withdrew consent or lost to follow-up before iCPD per iRECIST or death	Censored	Date of last adequate disease assessment	Discontinued from Study without Documented iCPD or Death

Table 1c: Censoring Rules for the OS

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

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

Table 2: Last Known Alive Date for the Overall Survival

Source Data	Conditions
Last date patient known to be alive from Long-Term 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 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

The primary efficacy analysis will be the confirmed ORR as assessed by BICR per RECIST v1.1, and its 2-sided 95% confidence interval, calculated using Clopper-Pearson's method.

Due to the Sponsor's decision to stop enrollment early, the sample size necessary to ensure a 95% level of confidence and a power of 90% will not be reached. Therefore, the test will be exploratory, and interpreted as such.

A table summarizing the number and percentage of subjects with a Best Overall Response (BOR) of CR, PR, SD, PD, or Not Evaluable will be presented. This table will also include the ORR and DCR, with their two-sided 95% CI calculated using the Clopper-Pearson method.

C. Secondary Efficacy Analyses

Methodology for DOR, PFS, OS, iPFS, iDOR. Estimates of median with 95% CIs will be computed using the Kaplan-Meier method. Kaplan-Meier graphs will be visually displayed. Median Time-to-Event will be estimated at the 50th percentile of the corresponding Kaplan-Meier estimates. The event-free rate with the two-sided 95% CIs using Greenwood's formula will be calculated for 3-month interval timepoints (e.g., 6, 9, 12 and 18 months). The reasons for censoring will be summarized categorically with the number and percentage of subjects tabulated.

DOR by BICR. A table summarizing the secondary endpoint of DOR by BICR will be produced for subjects with a confirmed BOR of CR or PR only, following the methodology presented above.

PFS by BICR. The secondary endpoint of PFS by BICR will be summarized following the methodology presented above.

Treatment Effect in Non-injected Target Lesions. The confirmed ORR in non-injected target lesions per RECIST v1.1 assessed by BICR measurements will be evaluated using the same approach as the primary efficacy analysis ORR.

Efficacy Assessments per RECIST v1.1 by Investigator. Analysis of ORR, BOR, DCR, DOR, and PFS based on RECIST v1.1 by Investigator assessment will be performed using the same methods described in the previous sections.

OS. The secondary endpoint of OS will be summarized following the methodology presented above.

iORR, iDOR, iPFS. Post-progression disease assessments of tumor response based on iRECIST by Investigator assessment will also be summarized. Analysis of immune objective response rate (iORR), immune duration of response (iDOR), and immune progression-free survival (iPFS) based on iRECIST by Investigator assessment will be performed using the same methods described in the previous sections.

The following efficacy figures will be generated using the confirmed BICR RECIST v1.1 BORs for subject level classification for the ITT Analysis set. Additional figures for the Investigator assessment and iRECIST assessments may be produced.

- A waterfall plot will be generated summarizing the best percent change in tumor burden of injected and non-injected target lesions from the Screening/Baseline target lesion assessment for each subject, for responders only:
  - Tumor burden as reflected by the sum of the diameters (SOD) of all target lesions, concerning 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.

- A Spider plot of the percent changes in tumor burden for target lesion measurements (including the sum of the diameters (SOD) of all target lesions, the longest diameters for extranodal lesions, and the short axis for lymph nodes) from the Screening/Baseline target lesion assessment over time.
  - Each BOR category will be displayed in different colors

- A Swimmer plot delineating the occurrence of the clinical outcomes of interest over time, including the following information:
  - Duration of study 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. The swimmer plot will display each Confirmed BOR category as a separate color.
  - Time to death

- Kaplan-Meier plots displaying time-to-event on DOR, PFS, OS, per RECIST v1.1 as assessed by BICR, and by Investigator:
  - Estimate of median and the corresponding two-sided 95% CIs for median

- Event-free rates at selected timepoints

- A Forest plot suggesting ORR and the associated two-sided 95% CI

- For the analysis of the potential difference in tumor shrinkage in injected and non-injected target lesions within the same subject, a waterfall plot delineating the maximal percentage reduction in SOD from baseline for injected and non-injected target lesions, respectively, will be provided.

Listings of efficacy-related data (by BICR or by Investigator) will include the following:

- All lesion assessments (target lesion, non-target lesion, new lesion).
- Response assessments.
- Time to events (DOR, PFS, OS)

D. Efficacy Analysis on Subgroups of Subjects

The below subgroup analysis (not limited to) for efficacy will be explored using forest plots of the calculated ORRs with their 95% CIs.

- Serum LDH at diagnosis (Elevated, Normal)
- BRAF mutation (Yes, No)
- Number of Lines of Prior Therapies (1, 2, ≥ 3. Note the categories can be modified based on the data).
- Best Response to Prior Anti-PD-L1 (CR, PR, SD, PD, NE, NA, Unknown)
- Clinical Disease Stage at diagnosis (M0/M1a/M1b, M1c/M1d)

E. Exploratory Efficacy Analysis

The performance of the statistical analysis for the exploratory efficacy endpoint is contingent on the availability of the data source. Given the response assessment based on itRECIST[3] by Investigator has not been collected, and that the RECIST v1.1 and iRECIST were deemed sufficient for the purpose of the response assessment in the study from the Medical's perspective, no exploratory efficacy analyses will be carried out for the exploratory phase 2 study.

IX. Safety Analyses

Safety analyses will use data from the Safety Analysis Set. Subjects will be analyzed according to the actual study treatment received (i.e., the actual treatment arm variable(s) in SDTM/ADaM).

A. Exposure

Exposure to CMP-001 and Nivolumab will be summarized separately with descriptive statistics for the number of doses received, the duration of treatment to each drug (weeks), the planned dose intensity, the actual dose intensity, and the relative dose intensity (%).

1. Duration of Treatment

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

DoT (weeks) = [min(last dose date + 21 days, 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 of subjects with dose modifications (e.g., Drug Delayed, Drug Withheld, Drug interrupted, Dose Reduced, Drug Permanently Withdrawn) with the reasons will also be summarized by study drug.

Listings will be provided with the information from the study drug administration eCRFs for 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.

B. Adverse Events

Adverse events should be recorded upon first occurrence and followed until resolution. A persistent AE is continuous and does not resolve between Q3W dosing visits and should be 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. Any recurrent AE should be reported as new AE each time the AE occurs. Worsening of an ongoing AE (i.e., an increase to higher grade) should be recorded as a new AE. Ongoing AEs that decrease in severity/grade should not be captured as new AEs.

Immune-mediated AEs can include events with an alternate etiology that were exacerbated by the induction of autoimmunity. In the EDC system, each AE is classified as immune-mediated or not by the Investigator.

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

Medical occurrences that begin before start of study treatment should be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section.

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

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 treatment 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: the eCRFs and the Serious Adverse Event (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.

Treatment-emergent adverse event (TEAE)

Pretreatment AEs are AEs that occur from the time of informed consent up to the first dose of study treatment (W1D1). A treatment-emergent adverse event (TEAE) is defined as an AE that started or worsened in severity on or after the date that study treatment was first administered (W1D1) until 100 days after the last dose of study treatment or a new cancer treatment is initiated, whichever occurs first.

Treatment-emergent adverse events will be coded using MedDRA (version 23.1 or later) and data will be summarized for the Safety Analysis Set. The number and percent of subjects reporting each TEAE will be summarized, as well as the number of TEAEs. A subject with 2 or more TEAEs within the same level of summarization (i.e., system organ class or preferred term) will be counted only once in that level using the most severe event or most related (for the relationship to study treatment tables).

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 row for All Grades as well as rows 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 grade is missing for a TEAE, the event will be counted as grade 3=severe in the TEAE summary tables. If relationship is missing for a TEAE, the event will be counted as related in the TEAE summary tables.

An AE preferred term reported by a subject more than once will be represented in the most severe category or most related (for the relationship to study treatment tables).

A TEAE summary table will be generated including the following (N (%)):

- Subjects with one or more TEAEs
- Subjects with TEAEs of grade 3 or higher

- Subjects with CMP-001 treatment-related TEAEs (includes TEAEs which are definitely, probably and possibly related and those with missing relationship)
- Subjects with Nivolumab treatment-related TEAEs (includes TEAEs which are definitely, probably and possibly related and those with missing relationship)
- Subjects with grade 3 or higher CMP-001 treatment-related TEAEs (includes TEAEs which are definitely, probably and possibly related and those with missing relationship)
- Subjects with grade 3 and higher Nivolumab treatment-related TEAEs (includes TEAEs which are definitely, probably and possibly related and those with missing relationship)
- Subjects with Serious AEs (SAEs)
- Subjects with CMP-001 treatment-related SAEs (includes TEAEs which are definitely, probably and possibly related and those with missing relationship)
- Subjects with Nivolumab treatment-related SAEs (includes TEAEs which are definitely, probably and possibly related and those with missing relationship)
- Subjects with TEAEs leading to CMP-001 treatment discontinuation
- Subjects with TEAEs leading to Nivolumab treatment discontinuation
- Subjects with immune-mediated AEs as assessed by the Investigator
- Subjects with TEAEs resulting in death

The following additional AE summaries by SOC/PT will be produced:

- All TEAEs
- Grade 3 or higher TEAEs
- TEAEs by maximum grade and maximum relationship
    - TEAEs related to any study drug (includes TEAEs which are definitely, probably and possibly related and those with missing relationship)
    - TEAEs related to CMP-001 (includes TEAEs which are definitely, probably and possibly related and those with missing relationship)
    - TEAEs related to Nivolumab (includes TEAEs which are definitely, probably and possibly related and those with missing relationship)
- TEAEs by maximum grade
- TEAEs by maximum relationship to CMP-001
- TEAEs by maximum relationship to Nivolumab

  - Grade 3 or higher TEAEs related to CMP-001 (includes TEAEs which are definitely, probably and possibly related and those with missing relationship)
  - Grade 3 or higher TEAEs related to Nivolumab (includes TEAEs which are definitely, probably and possibly related and those with missing relationship)
- TEAEs of Special Interest
- TEAEs resulting in death
- All SAEs
  - SAEs related to any study drug (includes TEAEs which are definitely, probably and possibly related and those with missing relationship)
  - SAEs related to CMP-001 (includes TEAEs which are definitely, probably and possibly related and those with missing relationship)
  - SAEs related to Nivolumab (includes TEAEs which are definitely, probably and possibly related and those with missing relationship)
- TEAEs leading to treatment discontinuation of any study drug
- TEAEs leading to CMP-001 treatment discontinuation
- TEAEs leading to Nivolumab treatment discontinuation

A hierarchical listing will display the MedDRA system organ classes represented in the data. Within each system organ class, the listing will display each unique preferred term. Within each preferred term, the listing will display each unique verbatim (recorded) term. Listed terms will be ordered alphabetically.

The following AE listings will be produced:

- All TEAEs
- Grade 3 or higher TEAEs
- TEAEs considered related to study treatment (includes TEAEs which are definitely, probably and possibly related and those with missing relationship)
- TEAEs resulting in death
- SAEs
- Related SAEs. This listing will include serious TEAEs with a drug relationship of “Possibly Related,” “Probably Related”, “Definitely Related.” It will also include serious TEAEs with missing drug relationships.
- TEAEs leading to treatment discontinuation

C. Clinical Laboratory Results

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.

Safety central laboratory data, including hematology, coagulation, serum chemistry, autoimmune lab panel and thyroid function tests (see Table 3), will be summarized using descriptive statistics (mean, standard deviation, median, minimum, and maximum) and presented for each time point, including change from Baseline, for the Safety Analysis Set. Shift tables from Baseline to the Max Post-Baseline Grade will also be created. Within normal limits and Normal will be used when appropriate for urinalysis parameters.

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.

Results from pregnancy tests will be provided in data listings.

Table 3: Clinical Laboratory Assessments

Hematology	Serum Chemistry	Urinalysis	Other Laboratory Tests
RBCs WBCs Differential WBC count Total leukocyte count, including differential Hemoglobin Hematocrit Platelets	Alanine aminotransferase (ALT) Albumin Alkaline phosphatase (ALP) Amylase Aspartate aminotransferase (AST) Bilirubin Blood urea nitrogen or serum urea Calcium Chloride Creatinine	Blood Glucose Nitrites pH Protein Specific gravity WBCs **Microscopic battery:** RBCs, WBCs, epithelial cells, casts (only if significant positive findings on urinalysis)	**Coagulation:** PTT PT INR **Thyroid Function Studies:** TSH, Free T3, Free T4 (at Screening) **Autoimmune laboratory Panel:** Anti-dsDNA Antinuclear

	Glucose Lactate dehydrogenase (LDH) Lipase Phosphorous Potassium Sodium Total protein		Antibody Antineutrophil cytoplasmic antibody Rheumatoid factor Antibodies to ribonucleoprotein (anti-RNP) **Tests to be performed as clinically indicated:** Adrenal function tests Human immunodeficiency virus Hepatitis B and C

Abbreviations: Anti-dsDNA = anti-double stranded DNA; RBC = red blood cell; T3 = triiodothyronine; T4 = thyroxine; WBC = white blood cell.
Note: Refer to the Study Laboratory Manual for additional information.

D. Vital Signs

Vital signs include measurement of blood pressure (systolic and diastolic blood pressure), respiratory rate, heart rate, and body temperature. Summaries of actual values and changes from baseline will be presented for each assessment time point, beginning with the first post-baseline assessment.

Moreover, 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

A by-subject data listing of all vital sign data will be generated.

E. 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.

F. Prior and Concomitant Medications

All medications administered to the subject from 30 days prior to first dose of study treatment (W1D1) until 100 days after discontinuation of both CMP-001 and Nivolumab will be recorded in the EDC. Treatment medications for AEs related to study treatment that occur more than 100 days after the last dose of study treatment will also be collected.

Documentation for each medication will include the generic name of the medication, route of administration, dates of administration, and indication for use. Combination drugs must be listed separately by each component study treatment and dose, when possible. Prior cancer treatments will be recorded separately.

Prior medications are those taken within 30 days of the first dose of study treatment and discontinued before the first dose of study treatment.

Concomitant medications are defined as medications which are taken during the course of study treatment and within 100 days of the last dose of study treatment. Additionally, medications started prior to the first dose of study treatment, but with a stop date after the first dose of study treatment and within 100 days of the last dose of study treatment will be considered concomitant medications.

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

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

A second hierarchical listing will display WHO Drug Anatomical Therapeutic Chemical class represented in the data. Within each anatomical class, the listing will display each preferred term. Within each preferred term, the listing will display each unique verbatim (recorded) term. Listed terms will be ordered alphabetically.

G. Prior and Concomitant Procedures

All procedures within 30 days of Week 1, Day 1 and through 100 days after last study treatment must be recorded in the EDC.

Prior procedures are defined as procedures with a procedure date that is prior to the first dose of study drug. Concomitant procedures are defined as procedures with a procedure date on or after the first dose of study drug, and within 100 days of the last dose of study drug.

Prior and Concomitant procedures will be presented in a by-subject data listing. The listing will contain both prior and concomitant procedures with an indication of whether the procedure is a prior or concomitant procedure. The listing will display entries from the Concomitant Procedures eCRF, ordered within subject by the "Procedure Start Date."

H. Electrocardiograms (ECGs)

ECG results (Heart Rate, PR Interval, QRS Interval, QT Interval, QTcF Interval), and classification of "Normal", "Abnormal, Not Clinically Significant", and "Abnormal, Clinically Significant" will be presented in data listings.

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 using 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

For the overall ECG result ("Normal", "Abnormal, Not Clinically Significant", and "Abnormal, Clinically Significant") summaries will be provided for baseline and each post-baseline assessment visit.

I. Eastern Cooperative Oncology Group Performance (ECOG)

Eastern Cooperative Oncology Group performance status (ECOG) results will be presented in data listings. ECOG at baseline will be presented in summary table of baseline characteristics. 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 for the Safety Analysis Set.

X. Pharmacokinetic Analyses

Per Sponsor's decision, no Pharmacokinetic analyses will be performed. The following exposes the root cause of this decision.

Section 9.7 of the protocol states the PK parameters that may be assessed include, but are not necessarily limited to, maximum observed serum concentration, time of maximum observed serum concentration, area under the serum concentration-time curve from time zero to the last quantifiable time point, area under the serum concentration-time curve from time zero extrapolated to infinity, and terminal elimination half-life.

Even though section 9.7 of the protocol indicates that PK parameters will be assessed in serum, the study lab manual instructs sites to collect PK using K2EDTA plasma tubes.

A method to determine the concentration of CMP-001 in serum was developed at Pace Labs. Samples (K2EDTA plasma samples) from this study were shipped and analyzed in March 2022 as an exploratory assessment. At the time, this analysis occurred since the samples were assumed to be human serum. Thus, the analysis results could not be interpreted since the method is specifically developed for serum. Plasma PK samples cannot be utilized to determine PK of CMP-001 as the data will not be valid for any future assessments.

XI. Pharmacodynamic Analyses

Concentrations of CXCL10 and other biomarkers will be summarized using descriptive statistics and listed for all time points for the Pharmacodynamic Analysis Set. Changes from Baseline will be included.

XII. Immunogenicity Analyses

Immunogenicity data based on anti-Qb antibodies will be summarized descriptively and listed for the Immunogenicity Analysis Set and Changes from Baseline will be included, provided that there are data available for the analysis set to be defined and analysis to be performed.

XIII. Exploratory Tumor Biopsy Analyses

Tumor biopsy obtained at Baseline and specified time points during the study will be summarized and listed 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.

XIV. 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. Hodi FS, Hwu WJ, Kefford R, Weber JS, Daud A, Hamid O, et al. Evaluation of immune-related response criteria and RECIST v1.1 in Patients With Advanced Melanoma Treated With Pembrolizumab. J Clin Oncol. 2016 May 1;34(13):1510-7.

3. 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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[redacted] [redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 10/11/2022 7:09:27 PM Viewed: 10/12/2022 9:40:06 AM Signed: 10/12/2022 9:41:59 AM
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Envelope Summary Events	Status	Timestamps
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Signing Complete	Security Checked	10/12/2022 9:41:59 AM
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Browsers:	• Internet Explorer (Windows Only) 8.0 or above – compatibility mode is supported only for 9.0 and above. • Windows Edge Current Version • Mozilla Firefox Current Version • Safari (Mac OS only) 6.2 or above • Google Chrome Current Version
PDF Reader:	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution:	1024 x 768 Recommended
Enabled Security Settings:	Allow per session cookies
Mobile Signing:	• Apple iOS 7.0 or above • Android 4.0 or above

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Pre-release (e.g. beta) versions of operating systems and browsers are not supported.

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