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Regeneron Pharmaceuticals Inc. / Protocol: CMP-001-007
IQVIA Biotech (Confidential) Project # SZA56629

Regeneron Pharmaceuticals, Inc.
Protocol #: CMP-001-007

A MULTICENTER, PHASE 2, OPEN-LABEL STUDY OF INTRATUMORAL CMP-001IN COMBINATION WITH INTRAVENOUS PEMBROLIZUMAB IN SUBJECTS WITH RECURRENT ORMETASTATIC HEAD AND NECK SQUAMOUS CELL CARCINOMA

Protocol Amendment 2 14 January 2022

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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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
ECOG	Eastern Cooperative Oncology Group
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

Head and neck cancer are the seventh leading cancer by incidence worldwide with approximately 890,000 new cases and 450,000 deaths each year. Squamous cell carcinomas of the head and neck constitute 90% of all head and neck cancers and are the ninth leading cancer by incidence worldwide. PD-1 blockade is an effective and important therapy for the treatment of HNSCC, however, more than 80% of patients do not respond to monotherapy treatment with an anti-PD-1 antibody. PD-1 negatively regulates T cell function when it interacts with its ligand PD-L1, which is commonly expressed on tumors. A major mechanism of resistance to PD-1 blockade is the absence of activated effector T cells in the tumor. Therefore, TLR9-mediated T cell activation and trafficking to tumor has the potential to improve the response to PD-1 blockade, particularly in non-inflamed tumors.

CMP-001 is intended to activate pDCs via TLR9 agonism, which causes the pDCs to release Type I IFN and take up and present tumor antigens to T cells, culminating in the generation of an antigen-specific, antitumor T cell response. Safety and efficacy data demonstrating the clinical benefit of CMP-001 IT in combination with pembrolizumab IV in patients with melanoma refractory to PD-1 blockade was obtained in an ongoing clinical trial, Study CMP-001-001.

This is a Phase 2 exploratory study to evaluate the safety and efficacy of intratumoral (IT) CMP-001 in combination with intravenous (IV) pembrolizumab in subjects with head and neck squamous cell carcinoma (HNSCC) with tumors that have a programmed death-ligand 1 (PD-L1) combined positive score (CPS) ≥ 1. The protocol for Study CMP-001-007 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 the Amendment 2 (version 3.0) of the Protocol CMP-001-007.

Version	Approval Date	Salient Changes, if any*
Initial	11 June 2020	
Amendment 1	03 August 2021	
Amendment 2	14 January 2022	Change in Schedule of Assessments

* Changes expected to require accommodation in analysis plan.

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 trial of CMP-001 IT in combination with pembrolizumab IV in subjects with recurrent or metastatic HNSCC. Eligible subjects must have histologically- or cytologically-confirmed recurrent or metastatic HNSCC considered incurable by local therapies. All subjects will receive CMP-001 IT and pembrolizumab IV according to the treatment schedule until a reason for treatment discontinuation is reached.

CMP-001 10 mg 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 drugs are administered, CMP-001 IT should be administered before pembrolizumab. 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 5.1.2.4 for treatment modifications for CMP-001. Pembrolizumab 200 mg IV will be administered following CMP-001 10 mg IT injection at W1D1 and Q3W thereafter according to the KEYTRUDA® USPI. Pembrolizumab treatment during this study will continue until the subject meets a condition for discontinuation of study treatment.

Objective responses will be assessed by the Investigator according to RECIST v1.1 and iRECIST. Disease status will be assessed by computed tomography (CT) or magnetic resonance imaging (MRI) and other appropriate measures beginning pre-dose at Week 10 Day 1 (W10D1) and will be repeated every 9 weeks (e.g., Week 19 Day 1). Responses (CR, PR, iCR or iPR) will be confirmed by a follow-up disease assessment

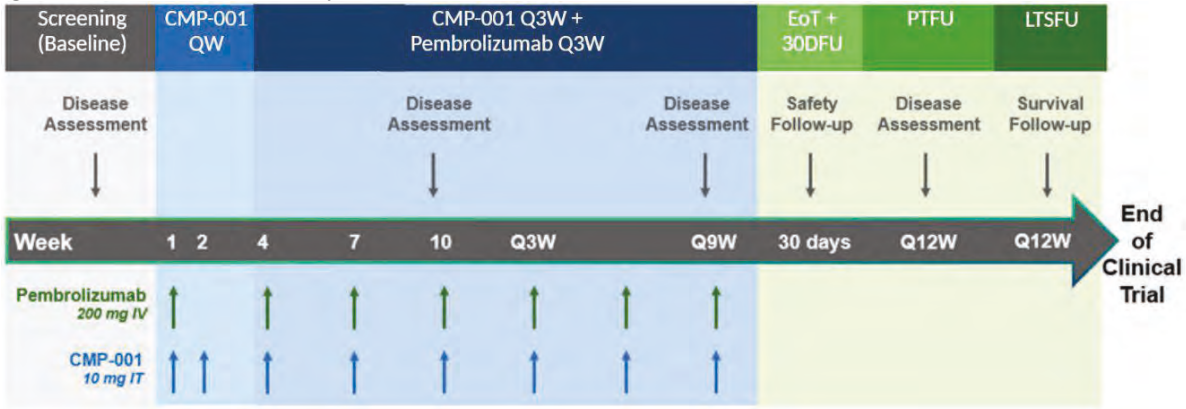
performed at least 4 weeks after the initial response date, and at least 2 weeks after the last CMP-001 injection. Disease assessments will continue every 9 weeks while the subject is on treatment. Disease assessments may continue every 12 weeks for subjects with a response lasting more than one year. Subjects who discontinue study treatment and transition into PTFU will continue to have assessments collected per the timepoints defined in the schedule of assessments.

Progressive disease (PD) will be assessed by the Investigator according to RECIST v1.1 criterion. Subjects who continue study treatment beyond PD according to RECIST v1.1 will be assessed by the Investigator according to iRECIST.

All scans should be performed at least 2 weeks after the previous CMP-001 IT injection to prevent injection-related pseudo progression. Imaging should not be delayed for delays in treatment.

Subjects who discontinue study treatment should complete the end of treatment (EOT) visit and 30-day safety follow-up. 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 (LTSF) and receive study evaluations for efficacy according to the Schedule of Assessments.

Figure 1: CMP-001-007 Study Schema



Abbreviations: 30DFU = 30-Day Follow-up; EOT = End of Treatment; LTSFU = Long-term Survival Follow-Up; IT = intratumoral; IV = intravenous; PTFU = Posttreatment Follow-up; Q3W = every 3 weeks; Q12W = every 12 weeks; QW = every week; SC = subcutaneous.
Note: The first dose of CMP-001 may be administered by SC or IT injection, per Investigator discretion. All subsequent doses of CMP-001 are planned to be administered IT.

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. The number of subjects included in this study is 24. Subjects who have provided written informed consent once the enrollment goal is reached may be allowed to complete Screening and enter study treatment if they meet all eligibility criteria, at the discretion of the Sponsor or its representatives. As enrollment is terminated, subjects who discontinue the study before receiving the first dose of CMP-001 will not be replaced.

With the enrollment of the last subject on 22Jun2022, the subject status of this study is as follows:

- 39 subjects were screened
- 15 subjects were screen failures
- 24 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 30 days of safety follow-up.

III. 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

- To determine the Investigator-assessed confirmed objective response with CMP-001 in combination with pembrolizumab in subjects with head and neck squamous cell carcinoma (HNSCC).

B. Secondary

- To evaluate the safety and tolerability of CMP-001 administered by intratumoral (IT) injection in combination with pembrolizumab in subjects with HNSCC.
- To evaluate the efficacy of CMP-001 in combination with pembrolizumab in subjects with HNSCC.
- To evaluate the effect of human papillomavirus (HPV) infection and programmed death-ligand 1 (PD-L1) expressions on the efficacy of CMP-001 in combination with pembrolizumab.

C. Exploratory

- To evaluate the effect of CMP-001 in combination with pembrolizumab on injected and noninjected target lesions in subjects with HNSCC
- To evaluate the pharmacodynamic and pharmacokinetic effects of CMP-001 administered in combination with pembrolizumab

IV. Study Endpoints

A. Primary

- Objective response rate (ORR), defined as the proportion of subjects with a confirmed objective response of complete response (CR) or partial response (PR) based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) as determined by Investigator assessment.

B. Secondary

- Adverse events (AEs), serious adverse events (SAEs), and AEs leading to discontinuation or death, and severity of AEs as assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0.
- Duration of response (DOR), defined as the time from date of first

documented response (CR or PR) to date of documented progressive disease (PD), based on RECIST v1.1 by Investigator assessment.

- Progression-free survival (PFS), defined as the time from date of first dose of study drug to date of documented PD based on RECIST v1.1 by Investigator assessment or death, whichever occurs first.
- Overall survival (OS), defined as the time from the date of first dose of study drug to the date of death.
- 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) by Investigator assessment.
- Immune progression-free survival (iPFS), defined as the time from date of first dose of study drug to date of iCPD by Investigator assessment or death, whichever occurs first.
- ORR, DOR, and PFS based on HPV status and PD-L1 expressions (combined positive score [CPS] ≥ 1 and CPS ≥ 20).

C. Exploratory

- Response in injected and noninjected target lesions per intratumoral 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 C-X-C motif chemokine 10 (CXCL10) (IP-10) after treatment with CMP-001
- Blood concentrations of CMP-001 or its metabolites

V. Interventions

A. Clinical Trial Material

Pembrolizumab is an FDA approved drug product for the treatment of patients with metastatic or unresectable, recurrent HNSCC whose tumors express PD-L1 [CPS ≥1] as determined by an FDA-approved test, and as a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy; therefore, subjects will be treated with commercial product of KEYTRUDA®. The physical characteristics of pembrolizumab are found in the KEYTRUDA® USPI.

CMP-001 is an investigational drug product 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 drug product are found in the current Investigator's Brochure and the Pharmacy Manual.

At each site closeout visit, a final drug accountability review and reconciliation must be completed, and any discrepancies must be investigated by site and Sponsor representatives, and their resolution documented. All remaining CMP-001 drug product vials will be destroyed onsite according to institutional SOPs, after discussion with the Sponsor or its representatives following the completion of site close out.

The protocol provides additional product details in Protocol Section 6.

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. MedDRA version 23.1 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 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 Pembrolizumab). Study Day 1 will be designated as the first day 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 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 known alive, 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 + 30 days, then the End-of-Treatment (EOT of the last study drug received) date + 30 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 be imputed as Dec 31st of the year of stop date.
- 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 Analyses

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 **Error! Reference source not found.** below as well as the safety analysis methods detailed in Section **Error! Reference source not found.** 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 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 Investigator
  - OS
  - Selected subgroup analysis
- Safety
  - Study drug exposure: CMP-001 and pembrolizumab
  - Prior and concomitant medications
  - Prior and concomitant procedures
  - All TEAEs (SAE, AESI)
  - Summary of clinical laboratory results
  - Summary of ECG results

H. Multiple Comparisons

No control for the effect of multiple comparisons is planned.

I. Analysis Sets

Three analysis sets will be defined for use with various analyses. 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	Tumor Biopsy
Treated	X	X	X	X		
Pharmacodynamic					X	X
All Screened		X				

1. Treated Analysis Set

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

2. 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.

3. All-Screened Analysis Set

The All-Screened Analysis Set is defined as all subjects who was screened including subjects who were screen failure.

J. Subgroups of Analysis Populations

1. HPV Status
   - Negative
   - Positive

2. PD-L1 Expression (Combined Positive Score, CPS)
   - $1 \leq CPS < 20$
   - $CPS \geq 20$

3. Schedule
   - A: Subjects under Schedule A are those who consented to protocol v1.0 and v2.0.
     - Per Protocol, subjects will receive CMP-001 10 mg weekly for 7 doses, after which CMP-001 will be administered every 3 weeks (Q3W), beginning on Week 10 Day 1 (W10D1), then on Week 13 Day 1 (W13D1), etc.
     - Subjects will receive Pembrolizumab 200 mg IV over 30 minutes following CMP-001 injection at Week 1 Day 1 (W1D1) and every 3 weeks thereafter (W4D1, W7D1, etc.) according to the

KEYTRUDA® (pembrolizumab) United States Prescribing Information. Pembrolizumab should be administered until the subject satisfies a condition for study treatment discontinuation.

- B: Subjects under Schedule B are those who consented to protocol v3.0, including those who reconsented to v3.0 from v2.0.
    - Per Protocol, subjects will receive CMP-001 10 mg weekly for 2 doses, after which CMP-001 will be administered every 3 weeks (Q3W), beginning on Week 4 Day 1 (W4D1), then on Week 7 Day 1 (W7D1), etc.
    - Subjects will receive Pembrolizumab 200 mg IV over 30 minutes following CMP-001 injection at Week 1 Day 1 (W1D1) and every 3 weeks thereafter (W4D1, W7D1, etc.) according to the KEYTRUDA® (pembrolizumab) United States Prescribing Information. Pembrolizumab should be administered until the subject satisfies a condition for study treatment discontinuation.

Efficacy in relation to HPV status and PD-L1 expression will be assessed and summarized for the Treated Analysis Set. Subgroup analysis based on Schedule will be performed where applicable.

K. 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 may be produced for outcome measures that involve extensive procedures to derive the analyzed outcomes, 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 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 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 follow IQVIA Biotech display standard including 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. Individual data listings will display all the relative values supporting corresponding table and figures.

VII. Subject Accountability

A. Subject Characteristics

Demography. Data collected about the following subject characteristics at the screening visit will be summarized for the Treated Analysis Set:

- Age. Age will be calculated as the number of years elapsed between birth date and the date of the ICF signature, 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 criteria, Follicle Stimulating Hormone (FSH) Result and Luteinizing Hormone (LH) Result
- Race
- Ethnicity

Additionally, subgroup analysis of demographics by schedule will also be performed. All demography data including informed consent date will be listed.

Baseline Characteristics. Height, baseline weight, baseline body mass index (BMI), and substance history will be summarized for the Treated Analysis Set and presented in a listing. Additionally, subgroup analysis of baseline characteristics by schedule will also be performed.

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

presented in a listing. Additionally, subgroup analysis of baseline disease characteristics by schedule will also be performed.

Medical History Other Than Head/Neck Cancer. Medical history will be summarized in a table and listed by subject for the Treated Analysis Set. Medical history will be coded using MedDRA, associating lower-level terms with preferred terms and system organ classes by the primary hierarchy.

Head/Neck Cancer History. Listings of all collected data related to Head/Neck cancer history will be provided for Treated Analysis Set. A summary table of the following elements (but not limited to) will also be provided.

- Primary Site
- AJCC Version used at time of diagnosis
- Tissue Diagnosis Confirmed by
- p53 mutation
- EGFR status
- kRAS
- Cyclin d1
- Grade at diagnosis
- 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
- PD-L1 status

Prior Cancer Treatments. The following information will be summarized for the Treated Analysis Set for the prior head/neck cancer treatments:

- Number of Lines of Prior Systemic Therapies
    - Continuously (mean [SD], median, Q1, Q3, min and max)
    - 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 Any Prior Systemic Therapy
- Regimen Best Response on the Most Recent 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 head/neck 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 head/neck 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 Treated 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 for all screened subjects. The primary reason for treatment(s) and study discontinuation will also be summarized for Treated Analysis Set. Additionally, subgroup analysis of disposition by schedule will also be performed. Subject disposition will be presented in a by-subject data listing.

Study treatment (CMP-001 only or both CMP-001 and Pembrolizumab) 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 24 weeks, and has received at least 2 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.

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 following study review process.

VIII. Efficacy Analyses

Efficacy analyses will use data from the Treated Analysis set. Disease status will be assessed by computed tomography (CT) or magnetic resonance imaging (MRI) and other appropriate measures beginning pre-dose at Week 10 Day 1 and will be repeated every 9 weeks (e.g., Week 19 Day 1). Responses (CR, PR, iCR, or iPR) will be confirmed by follow-up disease assessment performed at least 4 weeks after the date of initial response and should be at least 2 weeks after the last CMP-001 injection. Imaging should not be delayed for delays in treatment.

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 based on RECIST v1.1 as assessed by the Investigator. Per RECIST v1.1, CR or PR must be confirmed by a confirmatory assessment performed at least 4 weeks after the initial response.

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 Treated Analysis Set.

Subjects who discontinue due to death 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). Objective Response assessment evaluated after new anti-cancer treatment will not be considered for ORR calculation.

Best Overall Response (BOR). The best response based on RECIST v1.1 as assessed by the Investigator recorded from the date of first study drug until PD or death was be considered the BOR for a subject. The number and percentage of subjects within each BOR category (confirmed CR, confirmed PR, stable disease (SD), PD, or not evaluable) will be summarized for the Treated Analysis Set. Objective Response assessment evaluated after new anti-cancer treatment will not be considered for BOR calculation.

The best overall response (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 response of CR, PR, or SD per RECIST v1.1 as assessed by the Investigator. 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. Confirmation of SD is not required. OR assessment evaluated after new anti-cancer treatment will not be considered for DCR calculation.

Duration of Response (DOR). Duration of response will be based on RECIST v1.1 as determined by Investigator and calculated for confirmed responders. 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. 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 did 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. Censoring rules are detailed 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 Investigator or death from any cause, whichever occurs first.

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. 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. Censoring rules are summarized in Table 1a. If a subject meets the criteria for more than one censoring rule, PFS will be censored at the earliest censoring date.

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 at the time of analyses 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. The last contact date will be derived as 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 a best overall immune 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 pseudo-progression.

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 best overall immune 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 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.

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) per iRECIST 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.

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,	Event	Earliest date of tumor assessment documenting iUPD	iCPD per iRECIST

whichever is earlier			
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 Contact 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
Post-treatment follow-up eCRF questions	Use if record selected
End of study	Not lost to follow up
Start/end dates from drug administration record	Nonmissing 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 nonmissing parameter value
Physical examination	Evaluation performed marked as yes
12-Lead ECG	Evaluation performed marked as yes
ECOG performance status date	Nonmissing ECOG performance status
Start/end dates of adverse events	Nonmissing verbatim term
Start/end dates of concomitant medications and procedures	Nonmissing verbatim term

B. Primary Efficacy Analysis

The primary efficacy endpoint of ORR: The two-sided 95% CIs for the point estimates will be provided using Clopper-Pearson method.

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

The secondary efficacy endpoints include PFS, DOR, iORR, iPFS, iDOR and OS.

iORR. The two-sided 95% CIs for the point estimates will be provided using Clopper-Pearson method.

PFS, DOR, iPFS, iDOR, and OS. Estimates of median with 95% CIs will be computed using the Kaplan-Meier method. Kaplan-Meier curves will be plotted. 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.

Subgroup analysis for ORR, DOR, and PFS based on HPV status (Positive vs. Negative) and PD-L1 expressions (combined positive score [CPS] ≥ 1 vs. CPS ≥ 20) for the Treated Analysis Set will be performed using the same approach for the main analysis. Additionally, subgroup analysis of ORR, DOR and OS by schedule will also be performed.

The following efficacy figures will be generated using the Investigator reported RECIST v1.1 assessments on the Treated Analysis set. Additional figures for the iRECIST by Investigator assessments may be produced.

- A waterfall plot of best percent change in the tumor burden of injected and non-injected target lesions from the Screening/Baseline target lesion assessment for each subject.
    - 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.
    - The waterfall plot will display each BOR category as a separate color.

- A spider plot of the percent changes in the tumor burden of target lesion measruments (including the sum of 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.

- The spider plot will display each BOR category as a separate color.

- A swimmer plot delineating the occurrence of the clinical outcomes of interest over time, including the following information:
  - Duration on study treatment
  - Time to BOR based on RECIST v1.1 as assessed by Investigator, 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
  - The swimmer plot will display each BOR category as a separate color.

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

D. 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 Treated Analysis Set. Subjects will be analyzed according to the actual study treatment received.

A. Exposure

Exposure to CMP-001 and Pembrolizumab will be summarized separately for the Treated Analysis Set with descriptive statistics for the number of doses received, the average number of volumes injected per dosing visit, the duration of treatment for each treatment (weeks), the planned dose intensity, the actual dose intensity, the relative dose intensity (%), and the treatment compliance.

1. Duration of Treatment

Duration of treatment (DoT) of CMP-001 and Pembrolizumab 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 Pembrolizumab, 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. Treatment Compliance

Treatment compliance is calculated as the number of CMP-001/Pembrolizumab doses received/expected doses within the treatment period defined as time from first dose to last dose.

4. 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.

Additionally, subgroup analysis of drug dosing and intensities for subjects by schedule will also be performed. Listings will be provided with the information from the study drug administration eCRFs for CMP-001 and Pembrolizumab, 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 TEAE (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.

According to 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 30 days after the last dose of study treatment should not be recorded on the AE eCRF unless they are related to study treatment.

Serious adverse events and AEs resulting in discontinuation will be followed until 1 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 30 days after the last dose of

study treatment. AE data collection also ceases at the time a new cancer treatment is started per protocol section 8.3, whichever occurs first.

Treatment-emergent adverse events will be coded using MedDRA (version 23.1) and data will be summarized for the Treated 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. Therefore, related AEs include those which are definitely, probably and possible related and those with missing relationship.

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

- Subjects with TEAEs
- Subjects with TEAEs of grade 3 or higher
- Subjects with TEAEs Related to CMP-001 and/or Pembrolizumab
- Subjects with CMP-001-related TEAEs
- Subjects with pembrolizumab-related TEAEs
- Subjects with grade 3 or higher TEAEs Related to CMP-001 and/or Pembrolizumab
- Subjects with grade 3 or higher CMP-001-related TEAEs
- Subjects with grade 3 or higher pembrolizumab-related TEAEs
- Subjects with treatment-emergent Serious AEs (SAEs)
- Subjects with SAE Related to CMP-001 and/or Pembrolizumab
- Subjects with CMP-001-related SAEs
- Subjects with pembrolizumab-related SAEs
- Subjects with AE of Special Interest

- Subjects with TEAEs leading to CMP-001 and/or Pembrolizumab Treatment Discontinuation
- Subjects with TEAEs leading to CMP-001 treatment discontinuation
- Subjects with TEAEs leading to Pembrolizumab Treatment Discontinuation
- Subjects with TEAEs leading to study discontinuation
- Subjects with TEAEs resulting in death

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

- All TEAEs, by MedDRA SOC and preferred term
- Grade 3 or higher TEAEs, by MedDRA SOC and preferred term
- TEAEs by maximum severity, by MedDRA SOC and preferred term
- TEAEs Related CMP-001 and/or pembrolizumab by maximum severity, by MedDRA SOC and preferred term
- TEAEs Related CMP-001 by maximum severity, by MedDRA SOC and preferred term
- TEAEs Related Pembrolizumab by maximum severity, by MedDRA SOC and preferred term TEAEs by highest relationship to CMP-001 and/or Pembrolizumab, by MedDRA SOC and preferred term
- Grade 3 or higher TEAEs Related to CMP-001 and/or pembrolizumab by MedDRA SOC and preferred term
- Grade 3 or higher CMP-001-related TEAEs, by MedDRA SOC and preferred term
- Grade 3 or higher pembrolizumab-related TEAEs, by MedDRA SOC and preferred term
- Death due to TEAEs, by MedDRA SOC and preferred term
- Serious AEs (SAEs), by MedDRA SOC and preferred term
- Grade 3 or higher SAEs, by MedDRA SOC and preferred term
- Grade 3 or higher CMP-001-related SAEs, by MedDRA SOC and preferred term
- Grade 3 or higher pembrolizumab-related SAEs, by MedDRA SOC and preferred term
- SAEs related to treatment (possibly + probably + definitely), by MedDRA SOC and preferred term
- SAEs related to CMP-001 by MedDRA SOC and preferred term
- SAEs related to pembrolizumab by MedDRA SOC and preferred term
- TEAEs leading to CMP-001 and/or Pembrolizumab treatment discontinuation

- TEAEs leading to CMP-001 treatment discontinuation
- TEAEs leading to pembrolizumab treatment discontinuation
- TEAEs leading to study discontinuation by SOC and preferred term

Additionally, subgroup analysis for the overall summary of adverse events by schedule will also be performed. A by-subject AE data listing, including verbatim term, SOC, preferred term, severity, outcome, and relationship to treatment, will be provided. Listed terms will be ordered alphabetically within subject. Separate listings will be generated for deaths, SAEs and AEs leading to treatment and study discontinuation.

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 for the Treated Analysis Set. All deaths including deaths that occur within 30 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. Additionally, subgroup analysis for deaths by schedule will also be performed.

D. 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 below), 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 Treated Analysis Set. Shift tables from Baseline to the Min and Max Post-Baseline, the categories in the shift tables will be WNL, Low, and High. 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.

Table 3: Clinical Laboratory Assessments

Hematology	Serum Chemistry	Urinalysis	Other Laboratory Tests
Red blood cells (RBCs) White blood cells (WBCs) Differential WBC count Hemoglobin Hematocrit Platelets	Alanine aminotransferase (ALT) Albumin Alkaline phosphatase (ALP) Amylase Aspartate aminotransferase (AST) Bilirubin Blood urea nitrogen Calcium Chloride Creatinine Glucose Lactate dehydrogenase (LDH) 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:** PTT PT INR **Thyroid Function Studies:** Thyroid Stimulating Hormone, Free T3, Free T4 **Autoimmune laboratory Panel:** Anti-dsDNA Antinuclear Antibody Antineutrophil cytoplasmic antibody Rheumatoid factor Antibodies to ribonucleoprotein (anti-RNP) **Tests to be performed as clinically indicated:** 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.

E. 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.

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

Documentation for each medication will include the generic name of the medication, dose per administration, 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 study treatment and within 30 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 30 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 and summarized according to the Anatomical Therapeutic Chemical (ATC) class II and preferred term for subjects in the Treated Analysis Set. 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 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.

H. 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 30 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 form, ordered within subject by the "Procedure Start Date".

I. 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 Treated 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.

J. Eastern Cooperative Oncology Group Performance (ECOG)

Eastern Cooperative Oncology Group performance status (ECOG) results will be presented in data listings. ECOG PS 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 Treated 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. 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 chemokine or cytokine 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. 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.

XIII. References

None.

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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 7:18:23 PM Viewed: 10/12/2022 9:42:46 AM Signed: 10/12/2022 9:43:51 AM
Electronic Record and Signature Disclosure: Accepted: 4/11/2022 1:02:14 PM ID: [redacted] Company Name: IQVIA		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	10/11/2022 7:18:23 PM
Certified Delivered	Security Checked	10/12/2022 9:42:46 AM
Signing Complete	Security Checked	10/12/2022 9:43:51 AM
Completed	Security Checked	10/12/2022 1:33:15 PM

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Operating Systems:	Windows® 2000, Windows® XP, Windows Vista®; Mac OS® X
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

** These minimum requirements are subject to change. If these requirements change, we will provide you with an e-mail message at the e-mail address we have on file for you at the time the hardware and software requirements are revised.

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

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