CMP-001-007

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

Study Phase:	Phase 2
IND Number:	16695
Sponsor:	Checkmate Pharmaceuticals, Inc. 245 Main Street, 2nd Floor Cambridge, MA 02142 United States
Responsible Medical Officer:	[redacted]
Issue Date:	Original Protocol 11 June 2020 Amendment 2 (Version 3.0) 14 January 2022

INVESTIGATOR'S AGREEMENT

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

Protocol Number: CMP-001-007

I have read this protocol and agree to the following:

- I am thoroughly familiar with the appropriate use of the investigational drug, as described in this protocol, and any other information provided by the Sponsor including, but not limited to, the current Investigator's Brochure (IB) provided by the Sponsor.
- I will conduct the study in compliance with this protocol, with any future amendments, and with any other written study conduct procedures provided and reviewed and approved by the Sponsor or its representatives.
- I will conduct the study in accordance with the current US Food and Drug Administration (FDA)/applicable local regulations; International Council for Harmonisation (ICH) guidelines and any other applicable regulatory requirements; as well as Good Clinical Practice (GCP) standards (CPMP/ICH/135/95); the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the principles of GCP; all local ethical and legal requirements; and will complete the study within the time designated.
- I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study.
- I agree that the Sponsor or its representatives shall have access to any source documents from which electronic case report form information may have been generated.

_____

Printed Name of Investigator

_____ _____

Signature of Investigator Date

SPONSOR PROTOCOL APPROVAL

I have read this protocol and approve the design of this study:

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 20-Jan-2022 | 5:55 AM PST
[redacted]

20-Jan-2022 | 5:55 AM PST

[redacted]

Date

Checkmate Pharmaceuticals, Inc.

PROCEDURES IN CASE OF EMERGENCY

Emergency Contact Information

Name	Role in Study	Address and Telephone Number
Checkmate Pharmaceuticals, Inc.	Sponsor	245 Main Street, 2nd Floor Cambridge, MA, USA 02142 Phone: 617-682-3625
IQVIA Biotech	Medical Monitor 24-Hour emergency contact	Email: [redacted]

Serious adverse events (SAEs) should be recorded on an SAE Report Form and completed and submitted to IQVIA Biotech Safety preferably via email to: [redacted] or by fax to [redacted] as back up within 24 hours of awareness. Information including a detailed description of the event; date and time (24-hour clock) of event onset and resolution.

SYNOPSIS

Name of Sponsor/Company: Checkmate Pharmaceuticals, Inc.

Name of Investigational Product: CMP-001

Name of Active Ingredient: QbG10, a virus-like particle (VLP) that encapsulates G10, a cytosine linked to a guanine by a phosphate bond (CpG) oligodeoxynucleotide

Title of Study: A Multicenter, Phase 2, Open-Label Study of Intratumoral CMP-001 in Combination with Intravenous Pembrolizumab in Subjects with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma

Study Center(s): The study will be conducted at clinical sites in the United States

Phase of Development: Phase 2

Study Objectives:

Primary Objective:

- 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)

Secondary Objectives:

- 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

Exploratory Objective:

- To evaluate the pharmacodynamic and pharmacokinetic effects of CMP-001 administered in combination with pembrolizumab

Study Endpoints:

Primary Endpoint:

- 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

Secondary Endpoints:

- 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)

Exploratory Endpoints:

- 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) and other cytokines after treatment with CMP-001
- Blood concentrations of CMP-001 or its metabolites

Methodology:

This is a multicenter, open-label, Phase 2 clinical trial of CMP-001 administered by IT injection in combination with intravenous (IV) pembrolizumab in subjects with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) not previously treated with a PD-1 blocking antibody. This will be a Phase 2 study, with response and DOR assessments using RECIST v1.1 and iRECIST criteria according to Investigator assessment. All subjects will receive CMP-001 IT and pembrolizumab IV according to the treatment schedule until a reason for treatment discontinuation is reached.

Number of subjects (planned):

A total of 43 subjects is planned for this study. This is based on the following assumptions:

- A historical ORR of 19% with pembrolizumab monotherapy in subjects with HNSCC who have a CPS ≥1 and were not previously treated with a PD-1 blocking antibody (null hypothesis)
- An anticipated ORR of 35% with CMP-001 and pembrolizumab (alternative hypothesis).
- Power of 80% and one-sided alpha level of 0.05.

Diagnosis and main criteria for inclusion:

Inclusion criteria:

Subjects enrolled in the study must meet all of the following inclusion criteria to be eligible:

1. Subjects with histologically- or cytologically-confirmed recurrent or metastatic HNSCC considered incurable by local therapies, and subjects with T4 or N3 disease who are ineligible for or refusing local therapies.
2. No prior systemic therapy in the recurrent or metastatic setting. Systemic therapy as part of multi-modal treatment for locally advanced disease is allowed.
3. Primary tumor locations of oropharynx, oral cavity, hypopharynx, larynx, paranasal sinus, or HNSCC of unknown primary origin. Participants may not have a primary tumor site of nasopharynx (any histology).
4. Able to provide tissue from a core or excisional biopsy (fine needle aspirate is not sufficient). A newly obtained biopsy (within 90 days before the start of study treatment) is preferred but an archival sample is acceptable.
5. CPS ≥1 for PD-L1 on immunohistochemistry (IHC) of tumor tissue.
6. Have results of tumor HPV p16 by IHC for oropharyngeal or for unknown primary cancer.
7. Measurable disease as defined by RECIST v1.1, and both of the following:
   a. At least 1 lesion amenable to repeated IT injection.
   b. Documented disease progression in any lesion that was previously radiated in order to serve as a target lesion.
8. Adequate organ function based on most recent laboratory values within 3 weeks before the first dose of study drug on Week 1 Day 1 (W1D1):
   a. Bone marrow function:
      - neutrophil count ≥ 1,500/mm^3
      - platelet count ≥ 100,000/mm^3
      - hemoglobin concentration ≥ 9 g/dL
   b. Liver function:
      - total bilirubin ≤ 1.5 times the upper limit of normal (ULN) with the following exception: subjects with Gilbert Disease serum bilirubin ≤ 3 times ULN
      - aspartate aminotransferase and alanine aminotransferase ≤ 3 times the ULN or ≤ 5 times the ULN for subjects with active liver metastases
   c. Renal function: estimated (Cockroft-Gault) or measured CrCl ≥30 mL/min
   d. Coagulation
      - International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 times ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
      - Activated Partial Thromboplastin Time (aPTT) or partial thromboplastin time (PTT) ≤ 1.5 times ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
9. Age ≥ 18 years at time of consent.
10. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1 at Screening.
11. Capable of understanding and complying with protocol requirements.
12. Women of childbearing potential must have negative serum pregnancy test during Screening and be willing to use an adequate method of contraception (Section 4.3.2) from the time of consent until at least 120 days after the last dose of study drug.

13. Able and willing to provide written informed consent and to follow study instructions. Subjects unable to provide written informed consent on their own behalf will not be eligible for the study.

Exclusion criteria:

Subjects presenting with any of the following will not qualify for entry into the study:

1. Disease suitable for local therapy administered with curative intent.
2. Has PD within 3 months of completion of curatively intent systemic treatment for locoregionally advanced HNSCC.
3. Radiation therapy (or other non-systemic therapy) within 2 weeks before the first dose of study drug on W1D1.
4. Received prior therapy with PD-1 or PD-L1 blocking antibody therapy in the recurrent/metastatic setting. If PD-1 or PD-L1 blocking antibody therapy was given as part of curative intent therapy, it must be at least 1 year since receipt of PD-1 or PD-L1 blocking antibody.
5. Not fully recovered from adverse events (to Grade 1 or less [per CTCAE v 5.0]) with the exception of persistent alopecia, neuropathy, ototoxicity, hypothyroidism, pain, xerostomia, or dysphagia, due to prior treatment.
6. Received systemic pharmacologic doses of corticosteroids ≥ 10 mg/day prednisone within 30 days before the first dose of study drug on W1D1.
    a. Subjects who are currently receiving steroids at a prednisone-equivalent dose of ≤ 10 mg/day do not need to discontinue steroids prior to enrollment.
    b. Replacement doses, topical, ophthalmologic, and inhalational steroids are permitted.
    c. Stress-dose corticosteroids will be required in subjects with adrenal insufficiency (see Section 5.1.2.1.1.).
7. Active pneumonitis or history of noninfectious pneumonitis that required steroids.
8. Severe uncontrolled cardiac disease within 6 months of Screening, including but not limited to poorly controlled hypertension, unstable angina, myocardial infarction, congestive heart failure (New York Heart Association Class II or greater), pericarditis within the previous 6 months, cerebrovascular accident, implanted or continuous use of a pacemaker or defibrillator.
9. Known history of immunodeficiency.
10. Known additional malignancy that is progressing or required active treatment within the past 3 years. Exceptions include cancers that have undergone potentially curative therapy, e.g., basal cell carcinoma of the skin, squamous cell carcinoma of the skin, localized prostate cancer with prostate-specific antigen level below 4.0 ng/mL, in situ cervical cancer on biopsy or a squamous intraepithelial lesion on Papanicolaou smear, thyroid cancer (except anaplastic), in situ breast cancer, and adjuvant hormonal therapy for breast cancer > 3 years from curative-intent surgical resection.
11. Active autoimmune disease that has required systemic treatment in past 2 years; replacement therapy is not considered a form of systemic treatment.
12. Untreated, symptomatic, or enlarging central nervous system (CNS) metastases or carcinomatous meningitis.

13. Prior allogenic tissue/solid organ transplant.
14. Active infection requiring systemic therapy.
15. Known or suspected active infection with SARS-CoV-2 virus.
16. Known or suspected active infection with human immunodeficiency virus, hepatitis B virus, or hepatitis C virus (testing is not required unless suspected).
17. Received a live virus/attenuated vaccination within 30 days before the start of study drug on W1D1.
18. Received blood products (including platelets or red blood cells) or colony stimulating factors (including GCSF, GMCSF, or recombinant erythropoietin) within 14 days before the start of W1D1.
19. Any concurrent uncontrolled illness, including mental illness or substance abuse, which in the opinion of the Investigator, would make the subject unable to cooperate or participate in the trial.
20. Participation in another clinical trial of an investigational anticancer therapy or device within 30 days before the first dose of study drug on W1D1
    NOTE: Participation in the follow-up phase (receiving no study treatment) of a prior study is allowed.
21. Requires prohibited treatment (i.e., non-protocol specified anticancer pharmacotherapy, surgery, or conventional radiotherapy) for treatment of malignant tumor.
22. Has a life expectancy of less than 3 months and/or has rapidly progressing disease (e.g., tumor bleeding, uncontrolled tumor pain) in the opinion of the treating Investigator.
23. Received previous CMP-001 treatment.
24. Pregnant or breast-feeding or expecting to conceive or father children within the projected duration of the study, from the time of consent until at least 120 days after the last dose of study drug.

Investigational product, dosage, and mode of administration:

Subjects will receive CMP-001 10 mg weekly for 2 doses (W1D1 and Week 2 Day 1 [W2D1 (-2/+5 days)]), 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.). The first dose of CMP-001 may be administered subcutaneously (SC) or by IT injection at the discretion of the Investigator; all subsequent doses are planned to be administered by IT injection. See Section 5.1.2.5 for treatment modifications for CMP-001.

Subjects will receive pembrolizumab 200 mg IV over 30 minutes following CMP-001 injection at W1D1 and every 3 weeks thereafter according to the KEYTRUDA® (pembrolizumab) United States Prescribing Information. Pembrolizumab should be administered until the subject satisfies a condition for study treatment discontinuation. See protocol for treatment modifications for pembrolizumab.

Duration of treatment:

Subjects will continue study treatment until they reach a reason for treatment or study discontinuation. Clinically stable subjects may continue study treatment beyond RECIST v1.1 progression based upon Investigator judgement of potential benefit. Study treatment may not continue beyond 2 years from initial dose of study treatment.

If a subject achieves and maintains a confirmed CR or iCR by Investigator review, treatment with CMP-001 or the combination of CMP-001 and pembrolizumab may be discontinued at the Investigator's discretion once they meet both of the following criteria:

- Subject has been treated with both study drugs for at least 24 weeks
- Subject has received at least 3 doses of both study drugs beyond the date of the initial CR/iCR
  NOTE: 3 doses are required only if medically feasible in the Investigator's opinion – less than 3 doses are acceptable if the Investigator is not medically able to inject.

Subjects who discontinue study treatment should complete an 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 (LTSFU) and receive study evaluations for efficacy according to the Schedule of Assessments.

Subjects who discontinue CMP-001 and/or pembrolizumab treatment may not be retreated on this study.

Criteria for evaluation:

Efficacy:

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.

Objective responses will be assessed by the Investigator according to RECIST v1.1 and iRECIST. Subjects who continue study treatment beyond PD according to RECIST v1.1 will be assessed by the Investigator according to iRECIST.

Translational Assessments:

- Quantification of the concentration of cytokines and chemokines from blood of subjects obtained at time points specified in the Schedule of Assessments
- Analysis of CD3+CD8+ T-cell infiltrates or other multi-parameter assessment of the tumor microenvironment in tumor tissue obtained via fresh biopsy or from archival tumor tissue, and correlation with antitumor activity.
- Intra-subject changes in immune status from pretreatment to posttreatment may be evaluated by technologies such as RNA profiling, flow cytometry, or IHC using tumor biopsies of injected or non-injected lesions, collected before treatment and starting at 4 weeks after initiation of weekly CMP-001 treatment.

Safety:

Safety and tolerability will be assessed by evaluating the following:

- Treatment-emergent adverse events, which will be evaluated and assigned a grade using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0
- Vital signs (oral temperature, respiratory rate, pulse, systolic and diastolic blood pressure), and physical examination (including weight and body mass index)
- Clinical laboratory parameters (chemistry, hematology, urinalysis, coagulation, and thyroid function tests)

- 12-Lead electrocardiograms (ECGs)

Statistical methods:

Study analysis sets for safety and efficacy will include:

- Intent-to-Treat (ITT) Analysis Set: all subjects who receive at least 1 dose of study drug
- Safety Analysis Set: all subjects who receive at least 1 dose of study drug
- Pharmacodynamic Analysis Set: all subjects who receive at least 1 dose of CMP-001 and have at least 1 measurable biomarker at Baseline and after CMP-001 injection
- Pharmacokinetic Analysis Set: all subjects who receive CMP-001 and have evaluable samples at Baseline and after CMP-001 injection

Categorical variables will be summarized as the number and percentage of subjects within each category (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).

Data from all investigational sites will be pooled in the analyses.

A detailed statistical analysis plan (SAP) will be finalized before database lock and will document the analysis methods, data handling procedures, and other statistical analysis issues. Statistical analyses will be performed using SAS® software version 9.4 or higher.

Safety data, including vital signs, ECGs, laboratory test results, physical examinations, and AEs, will be summarized by assessment time points, as appropriate. Change from Baseline will be included in summary tables for laboratory, ECG, and vital sign parameters.

The primary efficacy analysis of confirmed ORR will be assessed according to RECIST (Version 1.1) by the Investigator for the ITT Analysis Set. Secondary efficacy analyses will include PFS, BOR, DOR, OS, iORR, iPFS, iDOR; efficacy in relation to PD-L1 expression CPS $\geq$ 1 and CPS $\geq$ 20, and HPV status will also be assessed and summarized for the ITT Analysis Set.

Table 1: Schedule of Assessments

Procedure or Assessment	Screening (Day -30 to Day -1)	W1D1	W2D1	W4D1	W4D2	Q3W (W7D1, W10D1, etc.)	End of Treatment (EOT)[a]	30-Day Safety Follow-up (30DFU)[b]	Posttreatment Follow-up (PTFU)[c] (Q3mo)	Long-Term Survival Follow-up (LTSFU)[d] (Q3mo)
Visit Windows	**n/a**	**n/a**	**-2/+5d**	**+3d**	**n/a**	**± 3d**	**+7d**	**+7d**	**± 2 weeks**	**± 4 weeks**
CMP-001 Injection (Dose Number)[e]		1 SC/IT	2	3		4+				
Pembrolizumab Dosing (Dose Number)[f]		1		2		3+				
Informed Consent	X									
Eligibility Criteria Assessment	X									
Demographics	X									
Head and Neck Cancer History	X									
Prior Cancer Treatments	X									
Medical History	X									
Alcohol and Tobacco Use History	X									
Physical Examination[g]	X	X	X	X		X	X			
Vital Signs[h]	X	X	X	X	X	X	X			
ECOG Performance Status	X	X		X		X	X			
Adverse Event Monitoring[i]	X	X	X	X	X	X	X	X	X	
Concomitant Medications[j]	X	X	X	X	X	X	X	X	X	
12-Lead ECG[k]	X	X					X			
Clinical Laboratory Tests (hematology, serum chemistry, urinalysis)[l]	X	X	X	X		X	X			
Coagulation Tests[l]	X	X		X		X				

Table 1: Schedule of Assessments (Continued)

Procedure or Assessment	Screening (Day -30 to Day -1)	W1D1	W2D1	W4D1	W4D2	Q3W (W7D1, W10D1, etc.)	End of Treatment (EOT)[a]	30-Day Safety Follow-up (30DFU)[b]	Posttreatment Follow-up (PTFU)[c] (Q3mo)	Long-Term Survival Follow-up (LTSFU)[d] (Q3mo)
Visit Windows	**n/a**	**n/a**	**-2/+5d**	**+3d**	**n/a**	**± 3d**	**+7d**	**+7d**	**± 2 weeks**	**± 4 weeks**
CMP-001 Injection (Dose Number)[e]		1 SC/IT	2	3		4+				
Pembrolizumab Dosing (Dose Number)[f]		1		2		3+				
Thyroid Function Tests[l]	X			X		X	X			
Autoimmune Laboratory Panel[l]	X						X			
Pregnancy Test and Follicle Stimulating Hormone[l]	X	X		X		X	X			
Exploratory Biomarker Sampling[m]		X		X	X	W7D1				
Exploratory Sampling for Pharmacokinetics[m]		X		X	X	W7D1				
Tumor Biopsy (known PD-L1 status)[n]	X					W7D1				
Blood Sampling for Cytokine and Complement[o]		X		X		W7D1				
Disease Assessment (Radiographic Imaging)[p]	X					W10D1 Q9W	X		X	
Disease Assessment (CNS Imaging)[p]	X					W10D1 Q9W	X		X	
Photographic Imaging[q]	X					W10D1 Q9W	X		X	
30-Day Follow-Up (Office or Phone Call)								X		
Long-Term Survival Follow-up Phone Call										X

Abbreviations: 30DFU = 30-day follow-up; CNS = central nervous system; CPS = combined positive score; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FSH = follicle stimulating hormone; HPV = human papillomavirus; iRECIST = immunotherapy Response Evaluation Criteria in Solid Tumors; LTSFU = long-term survival follow-up; MRI = magnetic resonance imaging; PTFU = posttreatment follow-up; RECIST = Response Evaluation Criteria in Solid Tumors; Q3W = every 3 weeks; W = week; WOCBP = women of child bearing potential.

a. EOT assessments to be performed within 7 days following subject discontinuation from study treatment. Removal of a subject from CMP-001 treatment is defined as the time in which the Investigator decides to discontinue study treatment. If a subject has CMP-001 dosing withheld for more than 3 consecutive doses for any reason during the Q3W dosing period, resumption of treatment must be discussed with the Medical

Monitor; otherwise, the subject will be discontinued from study treatment and will have all EOT assessments performed. End of Treatment occurs once the subject discontinues administration of CMP-001. Subjects can continue to receive pembrolizumab as standard of care but will no longer be considered in study treatment.

b. The 30-Day Follow-up is a safety follow-up visit that may be conducted in the study clinic OR via phone. This visit should occur 30 days (+7) after the EOT visit.
c. PTFU will be conducted every 3 months (± 2 weeks) for all subjects who discontinue study treatment but have not met criteria for study discontinuation. These subjects should remain on study and receive disease assessments every 3 months, until discontinuation.
d. LTSFU will be conducted every 3 months (± 4 weeks) after the EOT visit or the last disease assessment date in PTFU and may occur by phone call.
e. CMP-001 Injection Visits: Weekly Dosing (W1D1 and W2D1): The first dose of CMP-001 may be administered SC or IT, at the discretion of the Investigator; all subsequent doses are planned to be administered IT until no injectable lesions remain. A window of -2/+5 days is permitted for CMP-001 dosing on W2D1. Q3W Dosing (W4D1+): A window of ±3 days is permitted for CMP-001 dosing from W4D1 throughout the trial. When pembrolizumab is permanently discontinued, CMP-001 must also be permanently discontinued. Refer to Section 5.4 for Treatment Compliance.
f. Pembrolizumab dosing will begin on W1D1 and continue Q3W throughout the study. When CMP-001 injection and pembrolizumab dosing fall on the same day, the CMP-001 injection will be given before pembrolizumab dosing. Refer to Section 5.1.1 for Pembrolizumab Dosing.
g. A full PE will be conducted at Screening and EOT. If the Screening full PE is performed > 72 hours before the W1D1 visit, then a brief (symptom directed) PE must be performed within 72 hours before the first injection of CMP-001. Brief PEs focused on areas of disease or AEs must be performed at every CMP-001 injection visit, and at any other time as clinically indicated. Height will be obtained at Screening only and weight at all PE assessments.
h. Vital signs include measurement of blood pressure (systolic and diastolic blood pressure), respiratory rate, heart rate, and body temperature. Blood pressure and heart rate should be taken in the seated position following ≥ 3 minutes of rest. For the first 4 CMP-001 dosing visits (W1D1, W2D1, W4D1, and W7D1), vital signs must be collected before the CMP-001 injection and at 30 (± 15)-minute intervals for 4 hours after CMP-001 injection. Starting at W10D1, observation periods may be reduced to a minimum of 1 hour following CMP-001 injection at the Investigator's discretion based on the AE profile of the individual subject. When vital signs are scheduled at the same time as collection of a blood sample, the vital sign measurements should be obtained before the scheduled phlebotomy. If a study visit occurs where only pembrolizumab is administered, vital signs must be collected before the start of the pembrolizumab infusion.
   NOTE: Oxygen saturation is not a required parameter to be collected. Sites are to capture oxygen saturation every time an AE of hypoxia or cytokine release syndrome is reported for a subject.
i. Adverse events will be assessed continually from time of consent through 30 days after the last dose of study drug for all subjects. Subjects who discontinue CMP-001 but remain on treatment with pembrolizumab will continue to have AEs collected according to this schedule until 30 days after the last dose of pembrolizumab.
j. Concomitant medications will be assessed continually from time of consent through 30 days after the last dose of study drug. Treatment medications for study-related AEs that occur through 30 days after the last dose of study drug will be collected during the 30-Day Safety Follow-Up period.
k. 12-lead ECGs will be obtained at Screening, before the W1D1 CMP-001 injection, and at EOT. ECG parameters will include heart rate and PR, QRS, QT, and QT corrected for heart rate (QTc) intervals. ECGs will be performed after the subject has been resting in supine or semi-supine position for at least 5 minutes. When an ECG is scheduled at the same time as a blood sampling, the ECG reading should be obtained before the scheduled blood sampling.
l. Clinical laboratory assessments may be performed up to 72 hours before CMP-001 injection. When clinical laboratory assessments are done the same day as CMP-001 injection, vital signs should, if feasible/possible per site standard process, be performed before collection of clinical laboratory tests. Refer to Section 7.1.13 for Clinical Laboratory Assessments.
   NOTE: For WOCBP, a serum pregnancy test and FSH are completed at Screening. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours before the start of study treatment. An extension up to 72 hours before the start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window. Serum **or** urine pregnancy tests are also to be completed before CMP-001 injection on W1D1 and Q3W thereafter and EOT. Refer to Section 7.1.14 for Pregnancy Testing. An FSH test is required to confirm menopause in women with less than 12 months of amenorrhea (see Section 4.3.1). If fertility is unclear and a menstrual cycle cannot be confirmed before the first dose of study treatment (W1D1), subject should be considered of childbearing potential and applicable pregnancy tests completed.
   NOTE: Coagulation samples (PT, INR, and PTT) to be collected and results reviewed before CMP-001 injection at the W1D1 visit. Subsequent results are to be reviewed before every CMP-001 injection continuing Q3W thereafter beginning on W4D1 until EOT.
m. Exploratory biomarker and pharmacokinetic blood samples are to be collected at the following time points: pre-dose and 4 to 6 hours after CMP-001 injection on W1D1, W4D1, and W7D1. Optional collection 24 hours after CMP-001 injection on W4D1.
   NOTE: For sample collection on W1D1, W4D1, and W7D1, preference should be given to the later collection time point (i.e., 6 hours). Refer to Section 7.3.1 Collection of Blood for Translational Biomarker and Pharmacokinetics Analyses.
n. Fresh tumor biopsy samples are mandatory, if safe and medically feasible, at Screening or within 90 days (before W1D1) and W7D1 before CMP-001 IT injection. If the Investigator believes it is unsafe to perform a biopsy, the subject may be considered eligible after discussion with the Medical Monitor if tissue and/or prior assessments are available to determine PD-L1 expression and HPV status. Refer to Section 7.3.2 for Tumor Biopsies.
   NOTE: PD-L1 status is mandatory, and the combined CPS value must be recorded in the electronic case report form.
o. Blood samples for cytokine and complement assessment are to be collected at the following time points: 1) -2 to 0 hours before CMP-001 injection on W1D1, W4D1, and W7D1; 2) 4 hours (±30 minutes) after CMP-001 injection on W1D1, W4D1, and W7D1; and 3) if any AEs of cytokine release syndrome are experienced. Refer to Section 7.3.1 Collection of Blood for Translational Biomarker and Pharmacokinetics Analyses.
p. Disease assessment methods include radiographic imaging (CT or MRI) and CNS imaging by contrast-enhanced CT or MRI (per site local standards). The same modality used at Screening must be used throughout the study. Baseline CNS imaging should be provided for subjects with known or suspected brain metastases; on-study CNS imaging is required if symptoms or history of CNS disease is present at Baseline. Disease

assessments will be performed pre-dose beginning at W10D1 (-7 days) and repeated every 9 weeks (-7 days) (e.g., W19D1, W28D1). A response (CR, PR, iCR or iPR [per RECIST v1.1 or iRECIST]) will be confirmed with follow-up disease assessments performed at least 4 weeks after the date of initial response. Disease assessments will continue every 9 weeks after the confirmatory scans. Disease assessments may be performed every 12 weeks for subjects with a response continuing more than 1 year. All scans should be performed at least 2 weeks after the previous CMP-001 IT injection to prevent injection-related pseudoprogression. Refer to Section 7.2 for Disease Assessments.

q. If a subject has a visible lesion, digital photographs of CMP-001-injected and non-injected skin lesions should be taken at Baseline and if a clinically relevant change occurs. As part of disease assessment, photos should be taken at the same intervals as the radiographic imaging. Refer to Section 7.2.2 for Photographic Imaging.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
5-FU	5-fluorouracil
30DFU	30-Day Follow-Up
AE	adverse event
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BOR	best overall response
CFR	Code of Federal Regulations
CNS	central nervous system
CpG	cytosine linked to a guanine by a phosphate bond
CPS	combined positive score
CR	complete response
CRA	Clinical Research Associate
CT	computed tomography
CTL	cytotoxic T lymphocyte
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CXCL10	C-X-C motif chemokine 10
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
eCRF	electronic case report form
EOT	end of treatment
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HCC	hepatocellular carcinoma
HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation

Abbreviation or Specialist Term	Explanation
ID	identification
IEC	Independent Ethics Committee
IFN	interferon
INR	international normalized ratio
IRB	Institutional Review Board
iCPD	immune confirmed progressive disease
iCR	immune complete response
iORR	immune objective response rate
iPFS	immune progression-free survival
iPR	immune partial response
iRECIST	immunotherapy Response Evaluation Criteria in Solid Tumors
itRECIST	intratumoral Response Evaluation Criteria in Solid Tumors
iSD	immune stable disease
IT	intratumoral(ly)
ITT	intent-to-treat
iUPD	immune unconfirmed progressive disease
IV	intravenous
LTSFU	long-term survival follow-up
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
ODN	oligodeoxynucleotide
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
pDC	plasmacytoid dendritic cell
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PTFU	Posttreatment Follow-Up
PR	partial response
PS20	polysorbate 20
PT	protime
PTT	partial thromboplastin time

Abbreviation or Specialist Term	Explanation
Q3mo	every 3 months
Q3W	every 3 weeks
Qb	Qbeta
QTc	QT corrected
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	stable disease
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TLR9	toll-like receptor 9
ULN	upper limit of normal
UPD	unconfirmed progressive disease
US	United States
USPI	United States Prescribing Information
VLP	virus-like particle
WBC	white blood cell
WNL	within normal limits

1. INTRODUCTION

1.1. Background

This is a Phase 2 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.

Head and neck cancer is the seventh leading cancer by incidence worldwide with approximately 890,000 new cases and 450,000 deaths each year (Bray et al 2018). 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 (Jemal et al 2007; Gupta et al 2016). Head and neck cancers include cancers of the lip, oral cavity, oropharynx, hypopharynx, nasopharynx, larynx, as well as paranasal tumors, ethmoid sinus tumors, maxillary sinus tumors, salivary gland tumors, and mucosal melanoma head or neck tumors. In the United States, it is estimated that approximately 65,630 new cases of oral cavity, pharyngeal, and laryngeal cancers will occur in 2020, which account for approximately 3.6% of new cancers. An estimated 14,500 deaths from head and neck cancers will occur in the United States in the same time period (Siegel et al 2020).

Heavy use of alcohol and tobacco are typical etiologic factors in older patients. Human papillomavirus (HPV) infection, a well-accepted cause of squamous cancers of the oropharynx, has become more common, particularly in younger patients in North America and northern Europe (Chow 2020). The incidence of HPV-negative cancer has decreased; however, the overall incidence of HPV-positive head and neck cancers has increased in the United States, with the proportion of head and neck cancers diagnosed as HPV-positive rising from 16.3% in the 1980s to 72.7% in the 2000s (Chaturvedi et al 2008; Chow 2020). While oral HPV type 16 infection is the primary cause (Agalliu et al 2016; Gillison et al 2000; Gillison et al 2012; Ndiaye et al 2014), HPV types 18, 31, and 33 are responsible for the remaining HPV-related head and neck HPV-positive cancer (Snow and Laudadio 2010) and these primarily occur in younger patients. Two methods are used to detect HPV, polymerase chain reaction and p16 immunohistochemistry (IHC), with International Council for Harmonisation (ICH) testing being the more accessible established method (Duncan et al 2013).

NCCN guidelines on head and neck cancers (NCCN 2020) focused on head and neck cancers recommends participation in clinical trials for all patients with very advanced head and neck cancers. All combined chemoradiotherapy regimens are associated with mucosal toxicities. For patients with an ECOG Performance Status of 0 or 1, the NCCN guidelines on head and neck cancers (NCCN 2020) for newly diagnosed, very advanced disease is concurrent systemic/radiation therapy (with high-dose cisplatin and 5 fluorouracil [5-FU]) being a Category 1 option.

Response rates to systemic therapies range from 15% to 35% in patients with metastatic disease at initial presentation. In many circumstances, combination regimens result in a doubling of response rates compared to single agents but the median survival with systemic therapy is short (approximately 6 months) and a low 1-year survival rate of approximately 20% (NCCN 2020).

In KEYNOTE-048, pembrolizumab was evaluated as a first-line systemic treatment for patients with untreated, locally incurable recurrent or metastatic HNSCC (Burtness et al 2019). In this study, patients were randomized to receive pembrolizumab 200 mg every 3

weeks (Q3W) as a single agent (n = 300, monotherapy), the combination of pembrolizumab and chemotherapy consisting of a platinum and 5-FU (n = 276), or the combination of cetuximab, platinum, and 5-FU (n = 287, referred to as the EXTREME regimen). There was an overall survival (OS) advantage observed in the arm treated with the combination of pembrolizumab and chemotherapy with a median OS of 13 months compared to the EXTREME regimen with a median OS of 10.7 months (KEYTRUDA United States Prescribing Information [USPI]). Importantly, an OS advantage was also observed in patients with a PD-L1 CPS of both ≥ 20 and ≥ 1 for patients who received pembrolizumab monotherapy with a median OS of 14.9 months compared to those receiving the EXTREME regimen, where a median OS of 10.7 months was observed. The ORR for pembrolizumab monotherapy was 19% and 23% for the CPS ≥ 1 and CPS ≥ 20 groups, respectively, which was lower than the ORR observed with the EXTREME regimen of 35% and 36%, respectively. However, pembrolizumab monotherapy led to durable responses with a median duration of response (DOR) of 20.9 months for both CPS groups, which was longer than the 4.5 months and 4.2 months for the CPS ≥ 1 and CPS ≥ 20 groups in the EXTREME group, respectively.

In KEYNOTE-048, pembrolizumab was discontinued for adverse reactions in 12% of patients in the pembrolizumab monotherapy arm. The most common adverse reactions resulting in permanent discontinuation of pembrolizumab were sepsis (1.7%) and pneumonia (1.3%). Adverse reactions leading to the interruption of pembrolizumab occurred in 31% of patients. The most common adverse reactions leading to interruption of pembrolizumab (≥ 2%) were pneumonia (2.3%), pneumonitis (2.3%), and hyponatremia (2%). Based upon these safety and efficacy data, FDA approved pembrolizumab as first-line treatment for recurrent, unresectable, or metastatic HNSCC as monotherapy in patients with PD-L1 positive expressed tumors or when combined with a platinum and 5-FU. Despite this important advance, the majority of patients who received pembrolizumab did not achieve a response, and significant unmet need remains for new agents and combinations that achieve durable responses and prolong survival.

1.2. CMP-001

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. G10 is an ODN that contains CpG, and contains poly-G tails that allow it to form G-quadruplexes. Once administered to a subject, an antidrug antibody response to the VLP (anti-Qbeta 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 (Lemke Miltner et al 2020).

TLR9 is found in pDCs and B cells, but Type A CpG compounds have little effect on B cells. The pDCs primarily reside in blood but can also be found in tumors and lymph nodes. Unactivated tumor-infiltrating pDCs contribute to tumor growth and are associated with an adverse prognosis in subjects with cancer (Lombardi et al 2015; Demoulin et al 2013). Activation and maturation of pDCs through TLR9 agonism induces Type I interferons (IFN), which in turn mediate the release of IFN-inducible chemokines such as C-X-C motif chemokine 9 (CXCL9) and C-X-C motif chemokine 10 (CXCL10) (Swiecki and Colonna 2015). Activated pDCs also take up tumor specific antigens for presentation to T cells and other immune cells, facilitating the development of an antigen-specific, antitumor T cell

response. Together, the Type I IFNs, IFN inducible chemokines, and antigen presentation promote the activation and differentiation of $CD8^+$ T cells into cytotoxic T lymphocytes (CTL) capable of circulating throughout the body and attacking distant tumor cells. Therefore, administration of CMP-001 IT is hypothesized to change the pDC functional phenotype from tumor promoting to one that promotes an antigen-specific, antitumor $CD8^+$ T cell response.

1.2.1. Previous Clinical Studies With CMP-001

Safety and efficacy data demonstrating the clinical benefit of CMP-001 IT in combination with pembrolizumab IV in subjects with melanoma refractory to PD-1 blockade was obtained in an ongoing clinical trial, Study CMP-001-001, which is described in detail in the Investigator's Brochure (IB). In the 61 subjects who initiated treated with pembrolizumab according to the KEYTRUDA® (pembrolizumab) USPI in combination with CMP-001 10 mg IT QW × 7 and Q3W (Schedule A) thereafter with a preparation containing PS20 0.01%, the confirmed objective response Rate (ORR) was 23.1% (95% CI 5.0%, 53.8%) (Wong et al. 2021). A comparable response rate was observed in the 13 subjects treated with pembrolizumab in combination with CMP-001 10 mg IT QW × 2 and Q3W thereafter (Schedule B; Milhem et al. 2020; Kirkwood et al. 2021). This ORR is substantially higher than the 4% to 7% rate of pseudoprogression observed with continued PD-1 blockade after disease progression in other studies, and the recommended 6% to 7% for use as the null hypothesis for trials in this population (Hodi et al 2016; Ribas et al 2018). The clinical benefit of this combination treatment includes durable CRs and PRs in injected and non-injected target and non-target lesions of the skin, lymph nodes, and viscera. The current Kaplan-Meier estimate for median DOR for the 14/61 responders is 14 months (95% Confidence Interval = 6 months, not reached), which is described in detail in the IB.

1.3. Study Rationale

1.3.1. Rationale for Combining a TLR9 Agonist With an PD-1 Blocking Antibody

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 (Chen and Mellman 2013). 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.

In prior clinical trials, TLR9 agonism resulted in strong induction of CTL responses; however, very few objective responses were observed, and the T cell responses were not sustained, especially within tumors (Appay et al 2006). This may be because TLR9-mediated T cell activation induces PD-1 expression on activated T cells (Fourcade et al 2014). TLR9 agonists are capable of inducing tumor-specific $CD8^+$ T cells in cancer subjects, but the expression of PD-1 on these T cells blocks their function. Therefore, PD-1 blockade may facilitate and sustain the TLR9-mediated activation of tumor-specific T cells.

Several nonclinical and clinical reports support the hypothesis that TLR9 agonism may enhance the antitumor response 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 et al 2014), providing a strong rationale for the use of the combination of TLR9 agonists and anti-PD-1 antibodies in cancer therapy.

Several TLR9 agonists have shown antitumor efficacy in mouse tumor models in combination with PD-1 blockade. In mice with MB49 bladder cancer, a CpG-B ODN in combination with anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) or anti-PD-1 increased survival, and PD-1 blockade plus CpG treatment was superior to either agent alone. CpG plus anti-CTLA-4 or anti-PD-1 increased the numbers of circulating tumor-specific CD107a-expressing, $CD8^+$ T cells as well as activated ($CD25^+FoxP3^-$) CD4 splenocytes. Furthermore, regulatory T cells were decreased in the tumor area of treated animals after anti-CTLA-4 or anti-PD-1 plus CpG therapy (Mangsbo et al 2010). Additionally, mice treated with a CpG-B TLR9 agonist in combination with PD-1 blockade in an ovarian cancer model also had improved survival (Duraiswamy et al 2013). Mechanistic studies in the PD-L1 resistant mouse tumor models including CT26 and MCA38 colon carcinoma and TSA mammary adenocarcinoma demonstrated that IT injection of a CpG-C ODN reversed resistance to PD-1 blockade by inducing the infiltration of activated $CD8^+$ T cells expressing IFN-g (Wang et al 2016). Finally, injection of CMP-001 IT in a mouse A20 lymphoma model reduced the growth of both injected and noninjected tumors and improved survival, and these antitumor effects were enhanced by combination with systemic anti-PD-1 therapy (Lemke Miltner et al 2020). The VLP appeared to contribute to the antitumor efficacy of CpG-A therapy, since a reduced antitumor effect was seen if the CpG-A TLR9 agonist was administered without the VLP.

Several studies evaluating the addition of TLR9 agonism to immune checkpoint inhibition have been conducted, and data with CMP-001 in combination with pembrolizumab in subjects with PD-1 refractory melanoma is described above. Presently, only one study has been reported in subjects with HNSCC. A Phase 2 study (SYNERGY-001/KEYNOTE-184, NCT02521870) with SD-101, a synthetic class-C CpG-ODN TLR9 agonist, administered IT in combination with pembrolizumab in subjects with advanced/metastatic HNSCC, demonstrated acceptable safety and clinical efficacy (Cohen et al 2019). Responses (PR) and disease control were observed in subjects with low PD-L1 status at Baseline (CPS ≥1–20); 2 subjects with unknown PD-L1 status achieved a best response of CR. ORR was 35% in subjects with HPV-positive tumors and 11% in subjects with HPV-negative tumors. The best ORR across all subjects and doses was 24.0% (13.1, 38.2), and DOR was immature.

1.3.2. Rationale for Intratumoral Administration of TLR9 Agonists

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. Administration of CMP-001 IT is intended to activate pDCs, and subsequently T cells, within the tumor and tumor-draining lymph nodes where tumor-specific antigen is most likely to exist. Systemic administration of TLR9 agonists is expected to result in uptake by the liver, spleen, and reticuloendothelial system, which may lead to suboptimal activation of pDCs in tumor and tumor-draining lymph nodes.

IT administration of CMP-001 is expected to activate resting pDCs thereby overcoming their tumor-promoting phenotype and ultimately inducing an antitumor $CD8^+$ T cell response in the tumor microenvironment. In preclinical models, IT dosing of TLR9 agonists was more effective than distant subcutaneous (SC) dosing, and induced regression not only in the directly injected tumor lesion, but also distant metastases (Heckelsmiller et al 2002; Shirota et al 2012; Lemke Miltner et al 2020).

1.3.3. Rationale for CMP-001 Dose and Schedule

In the Phase 1b study CMP-001-001, CMP-001 IT was evaluated at doses of 1 mg to 10 mg using 2 dosing schedules and with preparations containing 2 different concentrations of the excipient polysorbate 20 (PS20) (0.01% and 0.00167%) in combination with pembrolizumab IV and as monotherapy in subjects with PD-1 refractory melanoma. The safety profile was similar and manageable across CMP-001 doses of 1 to 10 mg. Clinical activity, including durable complete and partial responses, was observed with CMP-001 10 mg (PS20 0.01%) IT weekly for 7 doses, followed by administration Q3W in combination with pembrolizumab IV (Schedule A) at the FDA-approved dose and schedule until treatment discontinuation. Comparable clinical activity was observed with an alternative schedule of CMP-001 administration in combination with pembrolizumab Q3W (Schedule B; Milhem et al. 2020; Kirkwood et al. 2021). The Schedule A dosing schedule and dose were selected for further development in refractory melanoma. As subjects with HNSCC often require radiology-assisted IT injections, the administration per modified Schedule B is introduced in this proof-of-concept study. Further details can be found in the IB.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of the study is to determine Investigator-assessed confirmed objective response with CMP-001 in combination with pembrolizumab in subjects with HNSCC.

2.1.2. Secondary Objectives

The secondary objectives of the study are to:

- Evaluate the safety and tolerability of CMP-001 administered by IT injection in combination with pembrolizumab in subjects with HNSCC
- Evaluate the efficacy of CMP-001 in combination with pembrolizumab in subjects with HNSCC
- Evaluate the effect of HPV infection and PD-L1 expressions on the efficacy of CMP-001 in combination with pembrolizumab

2.1.3. Exploratory Objective

The exploratory objective of the study is to evaluate the pharmacodynamic and pharmacokinetic effects of CMP-001 administered in combination with pembrolizumab.

2.2. Study Endpoints

2.2.1. Primary Endpoint

The primary endpoint is 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

2.2.2. Secondary Endpoints

The secondary endpoints are as follows:

- 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
- 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 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
- 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 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 PFS (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 and PD-L1 expressions (CPS ≥ 1 and CPS ≥ 20)

2.2.3. Exploratory Endpoints

The exploratory endpoints of the study are as follows:

- Response in injected and noninjected target lesions per intratumoral Response Evaluation Criteria in Solid Tumors (itRECIST) by Investigator assessment (Appendix F)
- 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) and other cytokines after treatment with CMP-001
- Blood concentrations of CMP-001 or its metabolites

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a multicenter, open-label, 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, and subjects with T4 or N3 disease who are ineligible for or refusing 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 2 doses, after which CMP-001 will be administered Q3W along with pembrolizumab, beginning from the next pembrolizumab dose on W4 until the subject meets a condition for discontinuation of study treatment or up to 2 years. 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 (Figure 1).

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 Appendix G). 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. See Section 5.1.2.5 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.

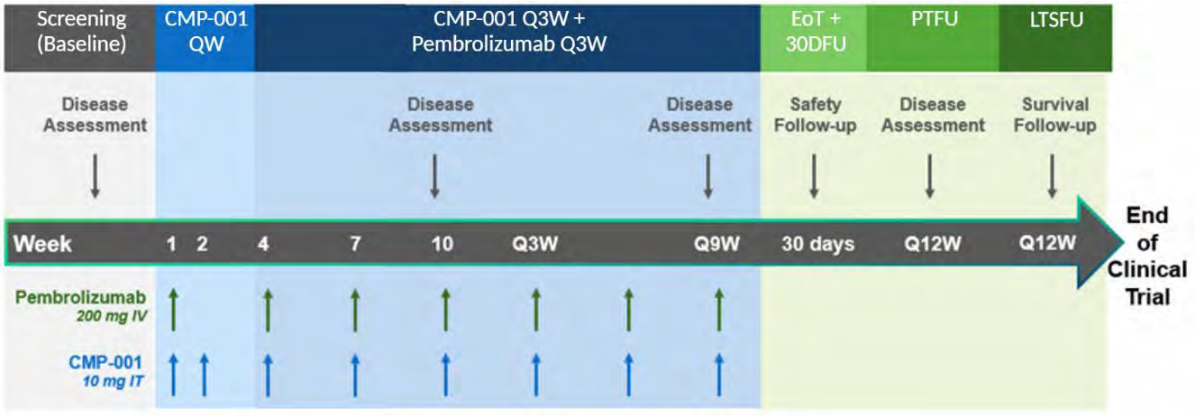
Objective responses will be assessed by the Investigator according to RECIST v1.1 and iRECIST. Disease status will be assessed by computed tomography (CT) or magnetic resonance imaging (MRI) and other appropriate measures beginning pre-dose at Week 10 Day 1 (W10D1) and will be repeated every 9 weeks (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. Progressive disease (PD) will be assessed by the Investigator according to RECIST v1.1 criteria. 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 pseudoprogression. 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 (LTSFU) and receive study evaluations for efficacy according to the Schedule of Assessments (Table 1).

There is no planned study extension beyond the 2 years of treatment.

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.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects will be eligible for this study if they meet all of the specified inclusion and none of the exclusion criteria.

4.1. Subject Inclusion Criteria

Subjects enrolled into this study must meet the following inclusion criteria to be eligible.

1. Subjects with histologically- or cytologically-confirmed recurrent or metastatic HNSCC considered incurable by local therapies, and subjects with T4 or N3 disease who are ineligible for or refusing local therapies.
2. No prior systemic therapy in the recurrent or metastatic setting. Systemic therapy as part of multi-modal treatment for locally advanced disease is allowed.
3. Primary tumor locations of oropharynx, oral cavity, hypopharynx, larynx, paranasal sinus, or HNSCC of unknown primary origin. Participants may not have a primary tumor site of nasopharynx (any histology).
4. Able to provide tissue from a core or excisional biopsy (fine needle aspirate is not sufficient). A newly obtained biopsy (within 90 days before the start of study treatment) is preferred but an archival sample is acceptable.
5. CPS ≥1 for PD-L1 on immunohistochemistry (IHC) of tumor tissue.
6. Have results of tumor HPV p16 by IHC for oropharyngeal or for unknown primary cancer.
7. Measurable disease as defined by RECIST v1.1, and both of the following:
   a. At least 1 lesion amenable to repeated IT injection.
   b. Documented disease progression in any lesion that was previously radiated in order to serve as a target lesion.
8. Adequate organ function based on most recent laboratory values within 3 weeks before the first dose of study drug on Week 1 Day 1 (W1D1):
   a. Bone marrow function:
      - neutrophil count ≥ 1,500/mm^3
      - platelet count ≥ 100,000/mm^3
      - hemoglobin concentration ≥ 9 g/dL
   b. Liver function:
      - total bilirubin ≤ 1.5 times the upper limit of normal (ULN) with the following exception: subjects with Gilbert Disease serum bilirubin ≤ 3 times ULN
      - aspartate aminotransferase and alanine aminotransferase ≤ 3 times the ULN or ≤ 5 times the ULN for subjects with active liver metastases
   c. Renal function: estimated (Cockroft-Gault) or measured CrCl ≥30 mL/min
   d. Coagulation
      - International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 times ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
      - Activated Partial Thromboplastin Time (aPTT) or partial thromboplastin time (PTT) ≤ 1.5 times ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

9. Age ≥ 18 years at time of consent.
10. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1 at Screening.
11. Capable of understanding and complying with protocol requirements.
12. Women of childbearing potential must have negative serum pregnancy test during Screening and be willing to use an adequate method of contraception (Section 4.3.2) from the time of consent until at least 120 days after the last dose of study drug.
13. Able and willing to provide written informed consent and to follow study instructions. Subjects unable to provide written informed consent on their own behalf will not be eligible for the study.

4.2. Subject Exclusion Criteria

Subjects presenting with any of the following will not qualify for entry into the study:

1. Disease suitable for local therapy administered with curative intent.
2. Has PD within 3 months of completion of curatively intent systemic treatment for locoregionally advanced HNSCC.
3. Radiation therapy (or other non-systemic therapy) within 2 weeks before the first dose of study drug on W1D1.
4. Received prior therapy with PD-1 or PD-L1 blocking antibody therapy in the recurrent/metastatic setting. If PD-1 or PD-L1 blocking antibody therapy was given as part of curative intent therapy, it must be at least 1 year since receipt of PD-1 or PD-L1 blocking antibody.
5. Not fully recovered from adverse events (to Grade 1 or less [per CTCAE v 5.0]) with the exception of persistent alopecia, neuropathy, ototoxicity, hypothyroidism, pain, xerostomia, or dysphagia, due to prior treatment.
6. Received systemic pharmacologic doses of corticosteroids ≥ 10 mg/day prednisone within 30 days before the first dose of study drug on W1D1.
    a. Subjects who are currently receiving steroids at a prednisone-equivalent dose of ≤ 10 mg/day do not need to discontinue steroids prior to enrollment.
    b. Replacement doses, topical, ophthalmologic, and inhalational steroids are permitted.
    c. Stress-dose corticosteroids will be required in subjects with adrenal insufficiency (see Section 5.1.2.1.1).
7. Active pneumonitis or history of noninfectious pneumonitis that required steroids.
8. Severe uncontrolled cardiac disease within 6 months of Screening, including but not limited to poorly controlled hypertension, unstable angina, myocardial infarction, congestive heart failure (New York Heart Association Class II or greater), pericarditis within the previous 6 months, cerebrovascular accident, implanted or continuous use of a pacemaker or defibrillator.
9. Known history of immunodeficiency.
10. Known additional malignancy that is progressing or required active treatment within the past 3 years. Exceptions include cancers that have undergone potentially curative therapy, e.g., basal cell carcinoma of the skin, squamous cell carcinoma of the skin,

localized prostate cancer with prostate-specific antigen level below 4.0 ng/mL, in situ cervical cancer on biopsy or a squamous intraepithelial lesion on Papanicolaou smear, thyroid cancer (except anaplastic), in situ breast cancer, and adjuvant hormonal therapy for breast cancer > 3 years from curative-intent surgical resection.

11. Active autoimmune disease that has required systemic treatment in past 2 years; replacement therapy is not considered a form of systemic treatment.
12. Untreated, symptomatic, or enlarging central nervous system (CNS) metastases or carcinomatous meningitis.
13. Prior allogenic tissue/solid organ transplant.
14. Active infection requiring systemic therapy.
15. Known or suspected active infection with SARS-CoV-2 virus.
16. Known or suspected active infection with human immunodeficiency virus, hepatitis B virus, or hepatitis C virus (testing is not required unless suspected).
17. Received a live virus/attenuated vaccination within 30 days before the start of study drug on W1D1.
18. Received blood products (including platelets or red blood cells) or colony stimulating factors (including GCSF, GMCSF, or recombinant erythropoietin) within 14 days before the start of W1D1.
19. Any concurrent uncontrolled illness, including mental illness or substance abuse, which in the opinion of the Investigator, would make the subject unable to cooperate or participate in the trial.
20. Participation in another clinical trial of an investigational anticancer therapy or device within 30 days before the first dose of study drug on W1D1
    NOTE: Participation in the follow-up phase (receiving no study treatment) of a prior study is allowed.
21. Requires prohibited treatment (i.e., non-protocol specified anticancer pharmacotherapy, surgery, or conventional radiotherapy) for treatment of malignant tumor.
22. Has a life expectancy of less than 3 months and/or has rapidly progressing disease (e.g., tumor bleeding, uncontrolled tumor pain) in the opinion of the treating Investigator.
23. Received previous CMP-001 treatment.
24. Pregnant or breast-feeding or expecting to conceive or father children within the projected duration of the study, from the time of consent until at least 120 days after the last dose of study drug.

4.3. Women of Childbearing Potential

A woman of childbearing potential (WOCBP) is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (Section 4.3.1). If fertility is unclear and a menstrual cycle cannot be confirmed before the first study drug dose (W1D1), subject should be considered of childbearing potential and applicable pregnancy tests completed.

A WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours before the start of study treatment. An extension up to 72 hours before the start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window.

4.3.1. Women of Non-Childbearing Potential

Female subjects must meet 1 of the following criteria to be considered of non-childbearing potential:

- Have undergone hysterectomy or bilateral salpingectomy/oophorectomy or bilateral tubal occlusion/ligation at least 1 month before Informed Consent.
- Are medically confirmed to be post-menopausal (cessation of regular menses for at least 12 consecutive months before W1D1 with no alternative pathological or physiological cause).
  Females with less than 12 months of amenorrhea must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL on 2 measurements performed 2 months apart

If fertility is unclear and a menstrual cycle cannot be confirmed before the first dose of study treatment (W1D1), subject should be considered of childbearing potential and applicable pregnancy tests completed.

4.3.2. Acceptable Methods of Contraception

Heterosexually active female subjects of childbearing potential must agree to use at least 2 forms of highly effective methods of contraception, including at least 1 barrier method for the duration of the study and at least 120 days after the last dose of study drug. Women should not donate eggs during this posttreatment period.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of < 1% per year when used consistently and correctly (i.e., perfect use) and include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine Device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

4.4. Prohibited Treatments

Medications intended solely for supportive care are allowed (i.e., antiemetics, analgesics, megestrol acetate for anorexia).

The following concomitant medications are prohibited:

- Concurrent anticancer therapy with agents other than the combination study drug therapy (CMP-001 + pembrolizumab) is not allowed at any time during the study.
- Agents known to have TLR9 antagonist activity are prohibited throughout the study. The current known antagonists are chloroquine, hydroxychloroquine, and quinacrine.
- Systemic pharmacologic doses of corticosteroids > 10 mg/day of prednisone equivalent are not permitted at the time of study enrollment. However, corticosteroid administration is allowed in the following circumstances:
  - In the treatment of subjects with known adrenal insufficiency (see Section 5.1.2.1.1. Consultation with the Medical Monitor is required before enrollment of subjects with adrenal insufficiency
  - For the management of immune-mediated toxicities
  - For palliation of pain, brain metastases, or other disorders (consultation with the Medical Monitor is required)
- Complementary medications to treat the disease under study (e.g., herbal supplements or traditional Chinese medicines).

4.4.1. Vaccinations

Given the potential for injection site reactions and flu-like symptoms, vaccination with a viral vector or mRNA vaccine should not be performed within 1 week of CMP-001 injection.

4.4.2. Concomitant Procedures

Palliative radiotherapy or palliative surgery may be allowed after Medical Monitor consultation to ascertain whether clinical progression has occurred. If the lesion(s) targeted for palliation are target lesions, then the anatomic site requiring palliation must be assessed for disease status.

4.5. Treatment Discontinuation

Study treatment should continue until 1 of the following occurs:

- Unacceptable adverse event that precludes further study treatment (see Section 5.1.2.5.4 and Section 5.1.3)
- 2 years of study treatment
- PD per RECIST v1.1; continuation of treatment through suspected pseudo-progression is permitted at the Investigator's discretion until confirmed PD per iRECIST (Section 7.2.5)
- Upon request of the Sponsor or regulatory agency
- Clinical disease progression

- If medically necessary in the opinion of the Investigator
- Subject withdraws consent for treatment (note that a subject who withdraws consent for additional study treatment and procedures but not for antitumor response will continue to be followed)
- Subject becomes pregnant or begins breastfeeding
- Subject is lost to follow-up
- Death
- End of Clinical Trial

Subjects who permanently discontinue treatment with pembrolizumab because of immune-mediated AEs must also permanently discontinue treatment with CMP-001.

Subjects will continue study treatment until they reach a reason for treatment or study discontinuation. Clinically stable subjects may continue study treatment beyond RECIST v1.1 progression based upon Investigator judgement of potential benefit. Study treatment may not continue beyond 2 years from initial dose of study treatment.

If a subject achieves and maintains a confirmed CR or iCR by Investigator review, treatment with CMP-001 or the combination of CMP-001 and pembrolizumab may be discontinued at the Investigator's discretion once they meet both of the following criteria:

- Subject has been treated with both study drugs for at least 24 weeks
- Subject has received at least 3 doses of both study drugs beyond the date of the initial CR/iCR
  NOTE: 3 doses are required only if medically feasible in the Investigator's opinion – less than 3 doses are acceptable if the Investigator is not medically able to inject.

Subjects who discontinue study treatment should undergo the EOT assessments per Table 1. Subjects who discontinue study treatment for reasons other than disease progression (per RECIST v1.1 or iRECIST by Investigator, or clinical PD per Investigator) should remain on study for PTFU (Section 7.6) and LTSFU (Section 7.7) and receive disease assessments according to the Schedule of Assessments (Table 1).

4.6. Study Withdrawal

Subjects may withdraw from the study at any time and without penalty or loss of future medical care, or any other benefits to which they are otherwise entitled. Subjects will be withdrawn from the study for any of the following reasons:

- Subject withdraws consent for the study
- Subject lost to follow-up
- Death
- End of clinical trial

For subjects who withdraw consent from overall study participation (not only study treatment) will not have the EOT visit, safety follow-up visits, or further evaluations performed.

4.7. End of Clinical Trial

The End of Clinical Trial (EOT) is defined as the last visit for the last subject on the trial. All data collection will cease in all subjects when End of Clinical Trial is reached.

5. TREATMENT OF SUBJECTS

5.1. Administration of Study Drug

5.1.1. Pembrolizumab

Subjects will receive CMP-001 10 mg IT injection followed by pembrolizumab 200 mg IV at W1D1 and every 3 weeks thereafter according to the KEYTRUDA® USPI. Pembrolizumab should be administered until the subject satisfies a condition for study treatment discontinuation (Section 4.5). On visits where both study drugs are administered, CMP-001 should be administered first followed by administration of pembrolizumab. There is no specified waiting period between the end of CMP-001 injection and the initiation of pembrolizumab infusion.

5.1.2. CMP-001

Subjects will receive CMP-001 10 mg weekly for 2 doses (W1D1 and W2D1), after which CMP-001 will be administered by IT injection Q3W (beginning on W4D1, then on W7D1, etc.). 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. On visits where both study drugs are administered, CMP-001 should be administered before pembrolizumab. There is no specified waiting period between the end of CMP-001 injection and the initiation of pembrolizumab infusion. CMP-001 should be administered until a reason for treatment discontinuation is reached (Section 4.5). See Section 5.1.2.5 for dose modifications for CMP-001.

5.1.2.1. Required Prophylaxis Before and After CMP-001 Injection

To reduce the incidence and severity of symptoms associated with CMP-001 injection, prophylaxis is required. All recommended prophylaxis should be administered before initiation of the CMP-001 injection. The medications are recommended for oral administration, but IV is acceptable at the discretion of the Investigator. There is no waiting period between the end of prophylaxis and the start of the CMP-001 injection.

The optimal recommended regimen that has been effective for the treatment of CMP-001-associated AEs, should include all the following components:

- Intravenous fluids (e.g., approximately 1000 cc IV normal saline). The rate, volume, and substation fluids are at the Investigator's discretion
- Antipyretics (e.g., acetaminophen 1000 mg and a non-steroidal anti-inflammatory agent such as indomethacin 50 mg or ibuprofen 600 to 800 mg)
- Antiemetics (e.g., ondansetron 8 mg)
- Antihistamine (e.g., diphenhydramine 50 mg, with or without an H2-antagonist)
- Recommended hydrocortisone 25 mg at the Investigator's discretion. Subjects with adrenal insufficiency should be treated with stress dose steroids as described in Section 5.1.2.1.1.

It is also highly recommended to continue to administer IV fluids during the observation period immediately following the CMP-001 injection, rather than waiting to initiate fluids if hypotension is detected. Antipyretics, antiemetics, and antihistamines may be repeated at the Investigator's discretion.

Each medication given prophylactically before and after CMP-001 dosing must be recorded separately and for each visit.

5.1.2.1.1. Prophylaxis for Subjects with a History of Adrenal Insufficiency

Subjects with a history of adrenal insufficiency are at increased risk for moderate to severe AEs such as hypotension, which may occur within 1 to 4 hours after CMP-001 injection but may also occur outside this window. Subjects with known adrenal insufficiency may be allowed in the study.

At Screening, subjects previously treated with a CTLA-4 blocking antibody, subjects with clinical symptoms and/or laboratory findings suggesting risk for adrenal insufficiency, or subjects receiving corticosteroids with daily doses > 5 mg and ≤ 10 mg of prednisone equivalent for > 2 weeks should undergo diagnostic tests for adrenocorticotropic hormone (ACTH) and morning cortisol, and/or high-dose ACTH stimulation test (preferred testing method), if clinically indicated, via local laboratory, unless the diagnosis of adrenal insufficiency had been previously established.

All subjects with adrenal insufficiency must receive prophylactic stress-dose steroids (e.g., 50 to 100 mg hydrocortisone or equivalent orally every 8 hours) before and for 24 to 48 hours after each CMP-001 injection.

5.1.2.2. Observation Following CMP-001 Dosing

Subjects must be observed for at least 4 hours following each of the first 4 CMP-001 injections (W1D1 to W7D1). Beginning with the fifth CMP-001 injection (W10D1), the observation period may be reduced to a minimum of 1 hour following CMP-001 injection at the Investigator's discretion based on the AE profile of the individual subject.

5.1.2.3. CMP-001 Injections

5.1.2.3.1. Tumor Selection

Cutaneous, SC, and/or nodal tumors that are visible, palpable, or detectable by ultrasound guidance are acceptable for IT injection. Refer to Appendix G for CMP-001 injection guidelines.

Vigilance should be used when selecting lesions for injection that are in close proximity to critical structures (e.g., major airways).

Special attention and judgement should be exercised before injection of a lesion in the following areas: the "mask areas" of the face (central face, eyelids, eyebrows, periorbital nose, lips [cutaneous and vermilion], chin, mandible, preauricular and postauricular skin/sulci, temple, ear, genitalia, hands, and feet).

Tumors should be at least 0.5 cm in longest diameter and need not be the largest lesion. A visceral tumor may be injected with or without the use of interventional radiology if, in the opinion of the Investigator and after discussion with the Medical Monitor, it is the most appropriate site for IT injection. A preferred tumor for IT injection is an accessible lesion that is most rapidly progressing in the judgment of the Investigator.

When more than 1 tumor is amenable to IT injection, the Investigator may inject up to 3 tumors per CMP-001 treatment visit. The total dose of CMP-001 may be divided across the tumors at the Investigator's discretion, and the volume injected into each tumor must be recorded. The same tumor(s) should be injected each week during therapy, if possible. If an

injected tumor is clearly decreasing in size and another accessible non-injected tumor is not, then the Investigator may divide the CMP-001 dose between the 2 tumors or switch from injecting the regressing tumor to injecting the non-responding (or growing) tumor.

Subjects with metastatic disease who have regression of all injectable lesions, or who have an injection site reaction that precludes injection of the tumor, should receive CMP-001 SC near an original tumor (peritumoral) or in the area of the draining lymph nodes (see Appendix G).

5.1.2.3.2. Method of CMP-001 Administration

Topical or local anesthesia may be used at the Investigator's discretion.

See the Pharmacy Manual for guidance on selection of syringe and needles for CMP-001 IT and CMP-001 SC injection. For methods of CMP-001 administration see Appendix G.

5.1.2.4. Dose Modifications for CMP-001

The CMP-001 dose should remain unchanged during the study.

If a planned dose cannot be given on schedule due to a CMP-001 related toxicity, the injection should be delayed until the toxicity has improved or resolved. If a subject has CMP-001 dosing withheld for more than 3 consecutive doses for any reason during the Q3W dosing period, resumption of treatment must be discussed with the Medical Monitor; otherwise, the subject will be discontinued from study treatment and will have all EOT assessments performed.

If a planned pembrolizumab dose is delayed, the CMP-001 dosing may be delayed.

5.1.2.5. Management of Adverse Events Associated with CMP-001

Based on observations in earlier studies, CMP-001 has been associated with AEs such as injection site reactions (see Section 5.1.2.5.1) and flu-like symptoms. Flu-like symptoms could include fever, nausea, vomiting, chills, rigors, and/or hypotension. Additional symptoms may occur, such as headache, tachycardia, rash, and hypoxia. Symptoms should be expected within 1 to 4 hours following the injection but may also occur outside this window.

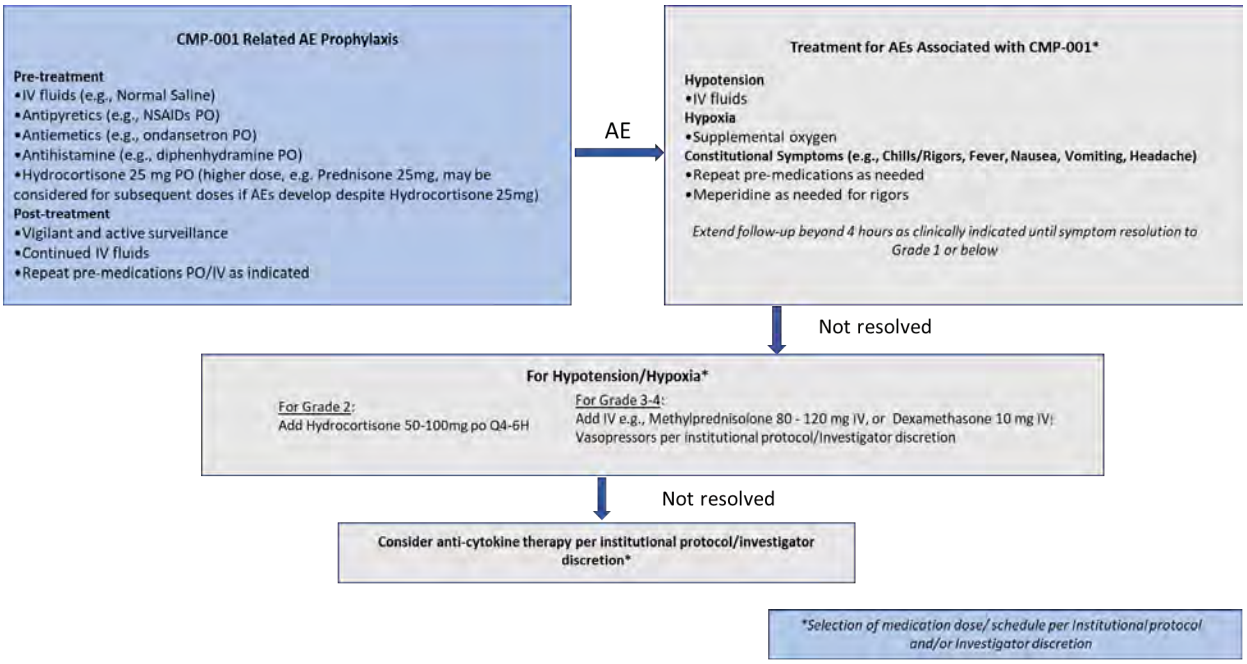
Sites are to capture oxygen saturation every time an AE of hypoxia or cytokine release syndrome is reported for a subject.

Required prophylaxis is designed to prevent or minimize the severity of these symptoms (see Section 5.1.2.1).

For additional safety information see the CMP-001 IB.

The following algorithm (Figure 2) is provided as guidance for prophylaxis and treatment of AEs associated with CMP-001.

Figure 2: Prophylaxis and Treatment for Adverse Events Associated with CMP-001



Abbreviations: IV = intravenous(ly); NSAID = non-steroidal anti-inflammatory drug; po = orally; Q4-6H = every 4 to 6 hours.

5.1.2.5.1. Allergic Reactions

Allergic reactions of an immediate type, including anaphylaxis, have been observed after CMP-001 administration. Please refer to the CMP-001 IB for a detailed description of a single case of anaphylaxis Grade 4.

Investigators must be vigilant in identifying and managing these disorders according to institutional guidelines. Precautionary measures consisting of pre-treatment prophylaxis and post-injection observation are in place to mitigate the risk of known adverse events associated with CMP-001, and these measures may prevent or lessen the potential for allergic reactions. Each site should have appropriate emergency equipment, medication, and skills necessary to diagnose and treat anaphylaxis and allergic reactions. CMP-001 should not be readministered to a subject who developed a suspected clinically significant allergic reaction without discussion with the Sponsor. The diagnosis and management of anaphylaxis should follow institutional guidelines.

5.1.2.5.2. Injection Site Reactions

Injection site inflammation is expected following the second and subsequent injections. If a subject develops inflammation at the injection site, this may be managed using cold compresses and medications for pain and inflammation, such as acetaminophen or non-steroidal anti-inflammatory agents. If, in the Investigator's opinion, a tumor cannot be injected due to injection site reaction or pain, refer to Section 5.1.2.3.1 on changing the site of injection.

5.1.2.5.3. Hypotension

If hypotension is unresponsive to IV fluids, stress dose steroids should be administered (Figure 2).

5.1.2.5.4. Grade 3 or Higher Adverse Events Related to CMP-001

For subjects who, despite optimal prophylaxis, experienced a Grade 3 or higher AE deemed related to CMP-001, prophylaxis with prednisone 25 mg or equivalent (at the Investigator's discretion) is required for subsequent CMP-001 doses. If treatment-related Grade 3 or higher hypotension, hypoxia, or cytokine release syndrome, or any treatment-related Grade 4 AE occurs despite premedication with 25 mg prednisone or equivalent, CMP-001 should be discontinued.

5.1.3. Adverse Events Associated with Pembrolizumab and Dose Modifications for Pembrolizumab

Pembrolizumab has been associated with a variety of AEs. The current KEYTRUDA® USPI should be consulted for treatment guidance on dose modifications. No dose reductions of pembrolizumab are recommended and specific treatment guidance is provided on withholding or discontinuing pembrolizumab to manage AEs. When pembrolizumab is permanently discontinued for an AE, CMP-001 must also be permanently discontinued.

5.1.4. Method of Assigning Subjects

Each enrolled subject will be assigned a unique Subject ID number using an Interactive Web Response System (IWRS). This number will be recorded on the subject's eCRF pages and used to identify the subject throughout the study. Once a subject number is assigned, it cannot be reassigned to any other subject. Subjects who discontinue the study before receiving the first dose of CMP-001 may be replaced to ensure at least 43 enrolled subjects.

5.2. Blinding and Unblinding Process

This is an open-label study. Investigator review will be used for assessment of the primary efficacy endpoint.

5.3. Prior and Concomitant Medications

IMPORTANT: Please refer to Section 5.1.2.1.1 for required prophylaxis before CMP-001 injection. Prophylaxis administered before and after CMP-001 dosing will be collected in the EDC for each visit.

Please refer to Section 4.4 for prohibited treatments.

Concomitant medications will be assessed continually from 30 days before the first dose of study drug (W1D1) through 30 days after the last dose of study drug. Treatment medications for study related AEs that occur through 30 days after the last dose of study drug will be collected. Subjects who discontinue CMP-001 but remain on treatment with pembrolizumab will continue to have concomitant medications/treatment medications collected according the Schedule of Assessments (Table 1).

In addition, at each LTSFU contact, an inquiry will be made regarding the start of any new cancer treatments since the date of the last contact. Prior cancer treatments will be documented on a separate eCRF.

5.4. Treatment Compliance

CMP-001 injections must be performed by qualified, trained, site personnel. Any deviations in planned dosing, including fully missed study visits, will be documented in the source

documents, verified by the Clinical Research Associate (CRA), and recorded as a protocol deviation as appropriate.

Pembrolizumab will be administered by trained site personnel at the clinic site according to the dosing instructions provided in the KEYTRUDA® USPI.

6. STUDY TREATMENT MATERIALS AND MANAGEMENT

6.1. Study Treatment

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 study drug. CMP-001 will be provided by the Sponsor as a 5 mg/mL solution in a single-use vial. Each single use vial will contain either 1 mL extractable volume, for a 5-mg dose of CMP-001, or 2 mL extractable volume, for a 10-mg dose of CMP-001. The physical characteristics and other details about the CMP-001 drug product are found in the current 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.

6.2. Study Treatment Packaging and Labeling

Details of the study drug labeling and packaging are provided in the CMP-001 Pharmacy Manual. The CMP-001 carton and CMP-001 study drug vials will be labeled with the following information:

- The protocol number
- The kit number
- Number of vials per kit (CMP-001 carton only)
- The batch number of the drug
- The drug name, concentration, and nominal volume per vial
- The recommended storage conditions of the drug
- Cautionary statement to keep away from children
- Cautionary statement indicating that the drug is for investigational use only
- The name and address of the Sponsor

6.3. Study Treatment Handling, Storage, Accountability

All CMP-001 drug product vials will be transported, received, stored, and handled in accordance with the drug product carton and vial labels, the Pharmacy Manual, the instructions, and training provided to the site and relevant personnel, the site's standard operating procedures (SOPs), and applicable regulations. Appropriate storage and transportation conditions will be maintained for the CMP-001 drug product vials from the point of manufacture up to delivery of CMP-001. All shipments of CMP-001 drug product vials will include a temperature monitoring device that records required storage conditions for the vials at regular intervals for the entire time the shipment is in transit.

Upon receipt by the site, the designated site personnel will examine the shipment and temperature monitoring devices to verify the CMP-001 drug product vials were received in acceptable condition. Vials received in acceptable condition should be stored at the specified temperature (2°C to 8°C) in a locked area accessible only to designated site personnel until dispensed. Dispensed CMP-001 drug product vials will be stored in a limited access area under appropriate environmental conditions as defined in the Pharmacy Manual. Vials not received in acceptable condition should be immediately quarantined at the appropriate temperature (2°C to 8°C), and the site personnel must immediately notify the CRA. Such study drug material may not be used until the Sponsor, or its representative (e.g., CRA) has conveyed a determination about these specific CMP-001 drug product vials.

The designated site personnel will be responsible for maintaining accurate records of the quantity and dates of all study drug supplies received, dispensed, and returned, in accordance with applicable regulations and the site's SOPs. The quantity of study drug lost, destroyed, or otherwise unaccounted for must also be accounted for and documented.

All original CMP-001 drug product vials, whether empty or containing CMP-001 drug product, will be kept at the site. CMP-001 vials are single-use only; therefore, contents of partially used CMP-001 drug product vials may not be dispensed again, even to the same subject, nor relabeled or reassigned for use by other subjects. Unused CMP-001 drug product vials will be available for verification by the study monitor. Used vials will be destroyed onsite according to institutional SOPs after agreement with the Sponsor or its representatives.

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.

Refer to the pembrolizumab USPI for information on handling and storage (KEYTRUDA® USPI).

6.4. Study Drug Dispensing

CMP-001 will be dispensed, prepared, and administered according to applicable study-specific Pharmacy Manual and site SOPs. Details regarding the preparation, dilution, and administration of the CMP-001 is outlined in the Pharmacy Manual. Only eligible subjects participating in the study may receive CMP-001. Only authorized and qualified site staff may dispense, prepare, or administer CMP-001.

Pembrolizumab will be dispensed, prepared, and administered according to the KEYTRUDA® USPI and site SOPs.

7. STUDY ASSESSMENTS AND PROCEDURES

7.1. Procedures and Assessments

Assessments to be performed at Screening and throughout the study are specified in the Schedule of Assessments Table 1.

7.1.1. Informed Consent

Subjects must sign a written informed consent form (ICF) before the initiation of any study procedures and thereafter if there are any ICF changes. Subjects will be given a signed copy of the ICF to take home. Subjects unable to provide written informed consent on their own behalf will not be eligible for the study.

7.1.2. Eligibility Criteria

Subjects must meet all inclusion and exclusion criteria to be eligible for the study. Refer to Section 4.

7.1.3. Demographics

Demographic data will be collected during Screening. Demographic data will include date of birth, sex, ethnicity, and race (i.e., white, black, or African American, Asian, American Indian/Alaskan Native, Native Hawaiian/other Pacific Islander, or other).

7.1.4. Head and Neck Cancer History

Eligible subjects must have been diagnosed with a histologically- or cytologically-confirmed diagnosis of recurrent or metastatic HNSCC with primary tumor locations of oropharynx, oral cavity, hypopharynx, larynx, or paranasal sinus. Participants may not have a primary tumor site of nasopharynx (any histology). American Joint Committee on Cancer (AJCC) staging at the time of study entry is required.

7.1.5. Prior Cancer Treatments

Details regarding all prior cancer treatments, including drug generic name, dose (if available), route of administration, start date, end date, best response, and last response to prior therapy, will be documented on a separate page in the EDC. Combination treatments should be considered as a single regimen and recorded as such in the EDC. Data on prior surgical procedures related to HNSCC will be captured on the same eCRF.

7.1.6. Medical History

At Screening, a general medical history will be obtained, including chronic conditions and co-morbidities, relevant acute conditions, or infections; surgical procedures unrelated to HNSCC, and any reported conditions affecting major body systems during the 10 years before Screening.

7.1.7. Alcohol and Tobacco Use History

At Screening, a history and current use of alcohol and tobacco or nicotine products (e.g., cigarettes, vaping, chewing tobacco, etc.) will be obtained. Subjects should be asked for details about the type, quantity, and frequency of alcohol and tobacco or nicotine use.

7.1.8. Concomitant Medications

All medications (Section 5.3) administered to the subject from 30 days before the first dose of study drug (W1D1) until 30 days after discontinuation of both CMP-001 and pembrolizumab will be recorded in EDC. Documentation for each medication will include the generic name of the medication, total daily dose, route of administration, dates of administration, and indication for use. Combination drugs must be listed separately by each component product and dose. Prior cancer treatment will be recorded separately.

7.1.9. Physical Examination

Physical examinations, including height and weight, will be conducted as specified in the Schedule of Assessments (Table 1). A full physical examination will be conducted at Screening and EOT. If the Screening full physical examination is performed > 72 hours before the W1D1 visit, then a brief (symptom directed) physical examination must be performed within 72 hours before the first injection of CMP-001. Brief physical examinations focused on areas of disease or AEs may be performed at any clinically indicated time but must be obtained before each CMP-001 injection visit. Height will be obtained at Screening only and weight at all physical examination assessments.

7.1.10. Vital Signs

Vital signs will be conducted as specified in the Schedule of Assessments (Table 1). Vital signs include measurement of blood pressure (systolic and diastolic blood pressure), respiratory rate, heart rate, and body temperature. Blood pressure and heart rate should be taken in the seated position following ≥ 3 minutes of rest. When vital signs are scheduled at the same time as collection of a blood sample, the vital sign measurements should be obtained before the scheduled phlebotomy. If a study visit occurs where only pembrolizumab is administered, vital signs must be collected before the start of the pembrolizumab infusion. If an indwelling cannula is being used to obtain blood, blood pressure should be measured in the arm opposite to the cannula placement.

Oxygen saturation is not a required parameter to be collected. Sites are to capture oxygen saturation every time an AE of hypoxia or cytokine release syndrome is reported for a subject.

7.1.11. Eastern Cooperative Oncology Group Performance Status

At Screening, the ECOG Performance Status (Appendix A) will be assessed and must be either 0 or 1 for the subject to be eligible. The ECOG Performance Status will be assessed as specified in the Schedule of Assessments (Table 1).

7.1.12. Electrocardiogram

A single standard, 12-lead electrocardiogram (ECG) will be obtained as specified in the Schedule of Assessments (Table 1). Assessed ECG parameters will include heart rate and PR, QRS, QT, and QT corrected for heart rate (QTc) intervals. QT will be corrected using Fridericia's (QTcF) formula. ECGs will be performed after the subject has been resting in supine or semi-supine position for at least 5 minutes. When an ECG is scheduled at the same time as a blood sampling, the ECG reading should be obtained before the scheduled blood sampling. The ECG results will be interpreted at the site by a medically qualified person. If indicated, the ECG must be evaluated by a cardiologist or qualified internist.

7.1.13. Clinical Laboratory Assessments

Clinical laboratory tests will be performed as specified in the Schedule of Assessments (Table 1). Additional tests may be performed as clinically indicated.

Clinical laboratory parameters (Table 2) to be obtained include:

- Hematology, chemistry, and urinalysis assessments
- Coagulation (Partial thromboplastin time, Prothrombin time, and INR) assessments
- Thyroid function tests (thyroid stimulating hormone, free triiodothyronine, and free thyroxine) for clinical signs and symptoms of thyroid disorder
- Autoimmune panel
- Adrenal function tests, if indicated

  NOTE: At Screening, subjects assessed as at risk for adrenal insufficiency should undergo diagnostic tests for ACTH and morning cortisol, and/or high-dose ACTH stimulation test (preferred testing method), if clinically indicated, via local laboratory.
- HIV, Hepatitis C/B, if indicated

A central laboratory will be used for clinical laboratory safety assessments; local laboratories may be used for eligibility and treatment decisions. The central laboratory will provide collection supplies and perform analysis of clinical laboratory evaluations. Specimens will be appropriately processed, and laboratory reports will be provided to the Investigator. A summary of the number and volume of laboratory specimens collected at each study visit is provided in Appendix B.

The Investigator is responsible for reviewing central laboratory results and assessing all out-of-range findings as either clinically significant or non-clinically significant. Clinically significant laboratory results should be recorded in the eCRF as medical history if before CMP-001 dosing at W1D1, or as AEs following CMP-001 dosing at W1D1.

Table 2: 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 Albumin Alkaline phosphatase Amylase Aspartate aminotransferase Bilirubin Blood urea nitrogen Calcium Chloride Creatinine Glucose Lactate dehydrogenase Lipase Phosphorous Potassium Sodium Total protein	Blood Glucose Nitrites pH Protein Specific gravity WBCs **Microscopic Battery:** RBCs, WBCs, epithelial cells, casts (only if significant positive findings on urinalysis)	**Coagulation:** PTT PT INR **Thyroid Function Studies:** Thyroid stimulating hormone, Free T3, Free T4 **Autoimmune Laboratory Panel:** Anti-dsDNA, anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, rheumatoid factor, and antibodies to ribonucleoprotein (anti-RNP) **Tests to be performed as clinically indicated:** Human immunodeficiency virus Hepatitis B and C

Abbreviations: dsDNA = double-stranded DNA; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; RNP = ribonucleoprotein; T3 = triiodothyronine; T4 = thyroxine; WBC = white blood cell.
NOTE: Refer to the Study Laboratory Manual for additional information.

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value). Laboratory parameters and/or assessments that are included in the Schedule of Assessments (Table 1) may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

7.1.14. Pregnancy Testing

Pregnancy testing will be performed on WOCBP at the time points specified in the Schedule of Assessments (Table 1). A serum pregnancy test is required during screening. A serum or urine pregnancy testing will be completed for time points after Screening.

A WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours before the start of study treatment. An extension up to 72 hours before the start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window.

If a urine pregnancy test is positive at any time point, the test must be confirmed with a serum sample. If a serum pregnancy test is required based on a positive urine pregnancy test, serum test results must be confirmed as negative before enrollment or subsequent treatment of the subject. If the serum test confirms the subject is pregnant, they must have the EOT visit, and the pregnancy must be reported to the Medical Monitor.

7.2. Disease Assessments

Disease assessments (radiographic and CNS imaging) will be collected according to the Schedule of Assessments (Table 1). Acceptable assessment methods, definition of measurable disease, and selection of target and non-target lesions will be defined by RECIST v1.1 (see Appendix D).

The same disease assessment method(s) used to confirm eligibility during Screening (CT, MRI) should be used throughout the study for all disease assessments. Changes in imaging modalities may be acceptable with Medical Monitor approval if required for the subject's safety. All scans should be performed at least 2 weeks after the previous CMP-001 IT injection to prevent detection of injection-related pseudoprogression.

Photographic and/or radiographic images demonstrating disease progression on prior PD-1–blocking antibody treatment will be collected whenever available.

All disease assessments will be evaluated by the Investigator according to RECIST v1.1 (Appendix D) and iRECIST (Appendix E).

7.2.1. Radiographic Imaging

Contrast-enhanced CT and MRI are the only acceptable radiographic imaging modalities for disease assessment. Contrast-enhanced CT imaging is required when contraindications are not present. Contrast-enhanced CT assessments may be combined with positron emission tomography (PET) as long as disease status can be thoroughly assessed. Ultrasound imaging may be used for measurement of lesions for itRECIST (Appendix F).

A target lesion(s) not intended for intratumoral (IT) injections should be clearly labeled in the Baseline imaging.

7.2.2. Photographic Imaging

Digital photographs of visible CMP-001-injected and non-injected skin lesions should be taken at Baseline and if a clinically relevant change occurs. As part of disease assessment, photos should be taken at the same intervals as the radiographic imaging. These photographs will be utilized to demonstrate response in visible tumors. Photos should be taken with a digital camera of adequate resolution. To clearly capture the morphology of the tumor, both the skin lesion and the surrounding tissue should be included in the field of view. Care should be taken to ensure subject privacy. Each lesion should be clearly labeled with a unique identifier which must be used throughout the trial. A metric ruler must also be included in the photograph field of view as a size reference. Photographic imaging will be collected by the site staff and uploaded to the central image repository.

A target lesion(s) not intended for IT injections should be clearly labeled in the Baseline imaging.

If a CR is observed, sites should continue to obtain confirmation photographs according to the Schedule of Assessments (Table 1).

Refer to the photographic imaging guideline for further guidance.

7.2.3. Central Nervous System Imaging

Baseline brain imaging by contrast-enhanced CT or MRI (per site local standards) should be provided at Screening for subjects with known or suspected brain metastases. On-study brain

imaging is only required for subjects with current or prior history of brain metastases or clinical signs or symptoms of CNS disease.

The same modality of brain imaging should be utilized throughout the study for an individual subject.

7.2.4. On-Treatment Disease Assessment

On-treatment disease assessments will be collected per the time points specified in the Schedule of Assessments (Table 1).

Because the volume from the IT injection of CMP-001 and related inflammation may cause a tumor to transiently enlarge leading to an inaccurate assessment, disease imaging that includes a lesion injected with CMP-001 should not be performed within 2 weeks after the injection unless medically necessary.

7.2.5. Treatment and Disease Assessment Beyond Progressive Disease

Clinically stable subjects may continue to be treated beyond RECIST v1.1 progression at the Investigator's discretion. Subjects who receive study treatment beyond PD per RECIST v1.1 will have subsequent disease assessments evaluated using iRECIST by the Investigator. Clinically stable subjects may continue to be treated beyond RECIST v1.1 progression at the Investigator's discretion until PD is confirmed according to iRECIST. Treatment beyond progression is permitted only in subjects who are clinically stable (Seymour, 2017). An assignment of clinical stability requires that no worsening of performance status has occurred, that no clinically relevant increases in disease-related symptoms such as pain or dyspnoea occur that are thought to be associated with disease progression, and that no requirement for intensified management of disease-related symptoms exists, including increased analgesia, radiotherapy, or other palliative care. Disease assessments should continue according to the Schedule of Assessments (Table 1).

7.2.6. Confirmation of Response

Subjects with a CR or PR per RECIST v1.1 or iCR or iPR per iRECIST must have a confirmatory assessment performed at least 4 weeks after the initial response. All scans should be performed at least 2 weeks after the previous CMP-001 IT injection to prevent injection-related pseudoprogression.

Subjects with an iCR or iPR per iRECIST must also have a confirmatory assessment performed at least 4 weeks after the initial assessment where response was declared by the Investigator.

Once confirmed, subsequent assessments should continue according to the Schedule of Assessments (Table 1).

7.3. Translational Assessments

7.3.1. Collection of Blood for Translational Biomarker and Pharmacokinetics Analyses

Blood samples, including serum and/or plasma will be collected for exploratory biomarker and pharmacokinetic assessments as specified in the Schedule of Assessments (Table 1). The procedures for sample collection, processing, storage, and shipment are provided in the Laboratory Manual. Blood samples will be tested to determine concentration of CXCL10 and other cytokines before and during treatment with CMP-001 to

evaluate association with the observed clinical responses to study treatment. Samples may be used for additional exploratory analysis of biomarkers thought to play a role in head and neck cancer, cancer immunotherapy, or TLR9, including but not limited to concentration of serum/plasma analytes. These findings may be analyzed for association with observed clinical responses to the combination of CMP-001 and pembrolizumab, and subsequent exploration of factors associated with response or resistance to CMP-001 in combination with pembrolizumab. These samples may be also used for research to develop methods, assays, prognostics and/or companion diagnostics related to TLR9 agonism and cancer immunotherapy.

7.3.2. Collection of Tumor Biopsies for Translational Assessments Analyses

Fresh tumor biopsy samples are mandatory, if safe and medically feasible, at Screening or within 90 days (before W1D1) and W7D1 before CMP-001 IT injection, as specified in the Schedule of Assessments (Table 1). If the Investigator believes it is unsafe to perform a biopsy, the subject may be considered eligible for study enrollment after discussion with the Medical Monitor. The decision and rationale to forego biopsy samples should be clearly documented. Archival tumor biopsy samples should also be collected during Screening, if available.

Tumor biopsies will be used to assess PD-L1 expression and may be used to analyze tumor immune cell infiltrates, such as CD3+CD8+ T-cells. Biopsies may be used for additional exploratory analysis of biomarkers thought to play a role in head and neck cancer, cancer immunotherapy, or TLR9, including but not limited to techniques such as the Nanostring IO360 panel evaluating 46 RNA gene expression signatures, and may be used to determine the presence of DNA mutations associated with tumor resistance. These findings may be analyzed for association with observed clinical response, resistance and/or adverse events to the combination of CMP-001 and pembrolizumab.

Determination of PD-L1 status is mandatory. If tumor PD-L1 status has been obtained before study entry, this value and method (detection antibody) will be recorded in the eCRF. If tumor PD-L1 status has not been obtained before study entry and archival tissue is available, it should be obtained from the archival biopsy sample at Screening. The PD-L1 value will be recorded in the EDC.

Additional tumor biopsies may be collected at other time points at the discretion of the Investigator.

7.3.3. Collection of Blood Samples for Cytokine and Complement Assessment

Blood samples are to be collected at the time points specified in the Schedule of Assessments (Table 1). When possible, samples should be collected at the time that any AEs of cytokine release syndrome are experienced.

7.4. Safety Assessments

Safety will be assessed on an ongoing basis throughout this study. All safety assessments and AEs will be recorded on the appropriate eCRF and reported to the Sponsor or its representatives (as applicable). Medical occurrences that begin before the start of study treatment administration but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section. All treatment-emergent adverse events (TEAEs), defined as an AE that started or worsened in severity on or after the date of Informed Consent, will be graded according to CTCAE

version 5.0 (Appendix C) and coded using the Medical Dictionary for Regulatory Activities (MedDRA). Worsening TEAEs (i.e., increase to higher severity/grade) should be recorded as new AEs. Ongoing AEs with a decrease in severity/grade do not need to be captured as new AEs.

Abnormal vital sign measurements, clinical laboratory test results, and/or physical examination findings deemed clinically significant by the Investigator may be repeated, until the value returns to Baseline, within normal limits (WNL), or reaches a clinically stable endpoint, as determined by the Investigator. Any post-Baseline abnormal findings that are considered clinically significant by the Investigator will be recorded on the AE page of the eCRF. The Investigator is responsible for reviewing all clinical laboratory results.

7.4.1. Adverse Events

AEs should be monitored from the time of consent through 30 days after the last dose of study drug (both CMP-001 and pembrolizumab). Pretreatment AEs related to study procedures will be monitored from informed consent until the first dose of study drug (W1D1). After the subject is enrolled, all AEs will be captured on the eCRF.

See Section 8.3 for a full description of the collection and reporting of AEs during this study.

7.5. 30-Day Follow-Up Contact

The 30-Day Follow-up contact is a safety follow-up visit that should be conducted in the study clinic **or** via phone. The subject should be questioned for any new AEs, resolution of prior AEs, and use of concomitant medications, including other cancer treatments. No other safety assessments are required unless the Investigator identifies a new safety concern that requires further follow-up.

7.6. Posttreatment Follow-Up

Subjects who discontinue study treatment and transition into PTFU will continue to have assessments collected per the time points specified in the Schedule of Assessments (Table 1). Post treatment follow-up disease assessments will continue until disease progression, initiation of another cancer treatment, death, lost to follow-up, withdrawal of consent, or End of Clinical Trial.

7.7. Long-Term Survival Follow-Up

Subjects who discontinue study treatment and PTFU, will be contacted by the site according to the Schedule of Assessments (Table 1) for LTSFU, which will continue until death, withdrawal of consent, lost to follow-up, or End of Clinical Trial.

8. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

8.1. Adverse Events

8.1.1. Definition of an Adverse Event

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

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. The AE is documented only once unless the grade becomes more severe. If the grade becomes more severe the AE must be reported again with the new grade. Any recurrent AE should be reported as new AE.

Adverse events include:

- Changes in health status described by the subject or signs observed by the Investigator or medical staff.
- Test abnormalities (e.g., laboratory tests) that result in an alteration in medical care (diagnostic or therapeutic) and/or are considered clinically significant by the Investigator.

Disease progression, and associated hospitalizations, are not considered an AE or SAE in this study.

Abnormalities present at Baseline will be recorded as medical history and will only be considered AEs if they reoccur after resolution or worsen during the study.

8.1.2. Definition of a Serious Adverse Event

An SAE is any AE that fulfills 1 of the criteria outlined in Section 8.1.2.

Table 3: Criteria for Determination of Serious Adverse Events

Death	An adverse event (AE) that results in death. NOTE: In this study, deaths due to Disease Progression are not to be reported as SAEs.
Life-threatening AE	An AE that places the subject, in the view of the Investigator, at immediate risk of death from the AE as it occurred (i.e., does not include an AE that had it occurred in a more severe form, might have caused death).
Required or prolonged inpatient hospitalization[a]	An AE that results in an initial inpatient hospitalization or prolongs an existing hospitalization of the subject. If a subject is hospitalized as part of the clinical use of the study drug, a period of normal hospitalization will be outlined in the protocol or by the judgment of the Investigator. Hospitalizations longer than this period will be prolonged hospitalizations.
Persistent or significant disability/incapacity	An AE that results in a substantial disruption of a subject's ability to conduct normal life functions.
Congenital anomaly/birth defect	A congenital anomaly/birth defect that occurs in the offspring of a subject exposed to the study drug.
Important medical event	An AE which may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed above, in the opinion of the Investigator.

a. Planned hospital admissions or surgical procedures for elective procedures or for an illness or disease that existed before the W1D1 visit will not be captured as SAEs. If planned admissions or procedures occur at a time other than what was planned (i.e., due to an exacerbation in the preexisting illness or disease), they should be reported as SAEs.
Appendix C: CTCAE version 5.0

Examples of "important medical events" include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as with important medical events described above.

Events that meet SAE criteria must be recorded and reported regardless of expectedness or assessed association with study drug.

Hospitalization due solely to the progression of underlying HNSCC should not be reported as an SAE.

8.1.3. Definition of a Treatment-Emergent Adverse Events

A TEAE is defined as an AE that started or worsened in severity on or after the date that study drug was first administered (W1D1) until 30 days after the last dose of study treatment.

8.2. Evaluation of Adverse Events and Serious Adverse Events

The Investigator or designee is responsible for making an assessment as to the severity (CTCAE Grade), causality/relationship to CMP-001 and pembrolizumab separately, and outcome of AEs and SAEs (as defined in Section 8.2.3). Every attempt should be made to

provide the causality/relationship at the time at the time of reporting the SAE. In addition, the Investigator or designee must report any actions taken as a result of an AE or SAE separately for CMP-001 and pembrolizumab.

8.2.1. Adverse Event Severity/Grade

For each recorded AE or SAE, the Investigator or designee must provide an assessment of Severity/Grade using the CTCAE version 5.0 (Appendix C).

Note that severity is not the same as "seriousness" (defined in Section 8.1.2). Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

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.

Table 4: CTCAE Adverse Event Grades

Classification	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limited self-care activities of daily living
Grade 4	Life-threatening consequences: urgent intervention indicated
Grade 5	Death related to adverse event

Appendix C: CTCAE version 5.0

8.2.2. Relationship to Study Drug

For each AE or SAE, the Investigator will determine whether there is a reasonable possibility demonstrated by evidence that suggests a causal relationship between the study treatment and each AE according to the categories provided in Table 5 (see Appendix C). Attribution of AEs will be determined for each of the individual components (CMP-001 and pembrolizumab) of the study treatment. The Investigator may change their opinion of causality in light of follow-up information; if this occurs, the Investigator must amend the AE or SAE information in the EDC and on the paper SAE form accordingly.

Table 5: Classification for Adverse Event Causality

Classification	Definition
Unrelated	There is no suspicion of a causal relationship between exposure to the study drug regimen and the AE; another cause of the AE has been identified, no temporal association with study drug has been identified, or the study drug cannot be implicated
Possibly related	There is some evidence supporting the possibility of a causal relationship between study drug regimen exposure and the AE; an alternative explanation (i.e., concomitant drug or concomitant disease) is inconclusive, the temporal association with study drug is reasonable, and the causal relationship cannot be excluded
Probably related	An AE that has a timely relationship to the administrative of the investigational drug regimen and follows a known pattern of response, but for which a potential alternative cause may be present
Definitely related	There is strong evidence that there is a causal relationship between study drug regimen and the AE; the AE cannot be reasonably explained by an alternate explanation (i.e., concomitant drug or concomitant disease) and the temporal association with study drug is suggestive of a causal relationship

Abbreviations: AE = adverse event.
NOTE: CMP-001 and pembrolizumab must be assessed separately. An AE is considered related to treatment if the attribution is "possibly related", "probably related", or "definitely related."
Appendix C: CTCAE version 5.0

8.2.3. Classification of Adverse Event Outcome

Adverse event outcome describes the status of the AE at the last observation. The Investigator will document the outcomes of each AE using the categories provided in below Table 6.

Table 6: Classifications for Adverse Event Outcomes

Classification	Definition
Fatal	Termination of life as a result of an AE
Not recovered/not resolved	Subject has not recuperated, or the AE has not improved
Recovered/resolved	Subject has recuperated, the AE resolved, or returned to Baseline status / stabilized
Recovered/resolved with sequelae	Adverse event has resolved, but the subject has been left with symptoms or pathology
Unknown	Not known, not observed, not recorded, or refused

Appendix C: CTCAE version 5.0

8.2.4. Action Taken Related to Study Drug Administration Regarding the Adverse Event

The Investigator will provide the action taken regarding study treatment separately for CMP-001 and pembrolizumab in response to the AE. Refer to Section 5.1.2.5 and Section 5.1.3 for CMP-001 and pembrolizumab allowed dose modifications. Classification for each of the potential actions taken are provided in Table 7.

Table 7: Classifications for Actions Taken Related to Study Drug Administration Regarding an Adverse Event

Classification	Definition
No change	No change in administration of study drug
Study drug delayed	Temporary delay in administration of the study drug
Study drug withheld	One or more planned doses of study drug completely withheld (skipped)
Study drug permanently withdrawn	Administration of the study drug terminated (no further dosing)
Not applicable	Determination of a value is not relevant in the current context

8.3. Procedures for Recording and Reporting Adverse Events

The Investigator is required to report to the Sponsor or its representatives all AEs that occur during the clinical trial (Title 21 Code of Federal Regulations [CFR] Part 312.64[b] and ICH E6 entitled "Guideline to Good Clinical Practice") (ICH E6). At each study visit, subjects will be evaluated for new AEs and the status of existing AEs. TEAEs observed from the time of consent until 30 days after the last dose of study drug (both CMP-001 and pembrolizumab) are to be recorded on the AE page of the eCRF.

The date, time of onset, resolution, determination of seriousness, severity, action taken, outcome and relationship to CMP-001 and pembrolizumab will be recorded for all AEs. AEs starting more than 30 days after the last dose of study drug should not be recorded on the AE eCRF unless they are considered to be related to study treatment.

All AEs and SAEs experienced by a subject will be recorded on the appropriate eCRF. In addition, for all SAEs a paper SAE Report Form will be completed and submitted to IQVIA Biotech Safety preferably via email to: [redacted] or by fax to [redacted] as back up within 24 hours of awareness. Information including a detailed description of the event; date and time (24-hour clock) of event onset and resolution; determination of seriousness, severity, corrective treatment, outcome, relationship to study drug; and action taken regarding the study drug will be recorded. Vital signs, laboratory results, and other safety assessments noted in Section 7.4 will be recorded as AEs if they are determined to be clinically significant findings in the opinion of the Investigator. When possible, a diagnosis should be recorded as an AE, rather than symptoms or isolated laboratory abnormalities related to the diagnosis. A medical or surgical procedure is not an AE; rather the condition leading to the procedure should be recorded as the AE. If the condition is not known, the procedure must be recorded as an AE instead. Similarly, death is not an AE, but is rather the outcome of the AE(s) that resulted in death. If the AE(s) leading to death are not known, then death must be reported as an AE.

8.3.1. Reporting Serious Adverse Events

All SAEs and associated source documents must be reported in written or typed English via completion of the eCRF AE page and accompanying paper SAE Report Form to IQVIA Biotech Safety (following the same reporting process outlined in Section 8.3) within 24 hours of first knowledge of the event regardless of relationship to the study procedures or individual study drugs. The paper SAE Report form should be used to record pertinent information,

regarding the SAE. The Investigator is requested to supply as much detailed information as possible regarding the event at the time of the initial report.

SAEs will be collected from the time of consent until 30 days after the last dose of any study allowed drug treatment.

If at any time after the subject has completed participation in the study, the Investigator or study staff becomes aware of an SAE during the study reporting period that they believe is possibly, probably, or definitely related to either study drug (see Section 8.2.2), then the event and any known details must be reported promptly to the Sponsor or its representatives. The following reporting instructions must be followed.

At minimum, the Investigator will be asked to provide the following information:

- For the initial SAE notification, the Investigator must provide, at a minimum, basic information such as the protocol number, subject's year of birth or age at onset, subject identification (ID) number, period of study drug intake, event term, nature of the event, detailed description of the clinical course of the event, seriousness criteria, causality of the event to CMP-001 and pembrolizumab separately, and severity.
- In addition, the initial SAE information entered on the eCRF and paper SAE Report Form should include all pertinent known information about the SAE and the affected subject, such as the following: subject sex; description of the AE including reason for assessment as serious, and individual study drug information including doses, dates of dosing, and action taken with individual study drugs.

Follow-up information must be entered or uploaded into the eCRF system and paper SAE Report Form and sent to IQVIA Biotech Safety (following the same reporting process outlined in Section 8.3.1) within 24 hours of the Investigator's first knowledge of the new information. Follow-up SAE reports may describe the evolution of the reported events and any new assessment of their outcome and/or relationship to individual study drugs. Supporting documentation may be solicited from the site even if the SAE occurred at another institution. Such documentation may include copies of relevant subject/hospital records, and pathology or autopsy reports. For subject deaths, the cause of death is to be recorded as the SAE term. A death certificate and an autopsy report, if performed, should be submitted.

The Sponsor designee contact information is available for SAE reporting on a 24-hour basis and is reviewed during normal business hours. A paper SAE Report Form should be completed and submitted to IQVIA Biotech Safety within 24 hours of awareness.

8.3.2. Reporting Pregnancies

Female subjects or the partners of male subjects who become pregnant within 1 year of their last CMP-001 dose will be instructed to notify the Investigator immediately.

If the Investigator learns of a report of pregnancy at any time after the W1D1 visit, the Investigator must complete and submit a paper Pregnancy Report Form and report the pregnancy to the IQVIA Biotech Safety within 24 hours of awareness (following the same reporting process outlined in Section 8.3.1).

The Investigator will inform the subject that the Sponsor or its representatives is required to gather information regarding the course and outcome of a pregnancy that has occurred after exposure to a study drug. The progress of the pregnancy must be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If

the pregnancy results in the birth of a child, additional follow-up information may be requested.

The Investigator will be asked to obtain follow-up information no later than 2 months after the gestational period to obtain maternal/fetal/neonatal outcome and any other relevant information.

Follow-up information may be requested at additional time points. All study-related contacts involving a known pregnancy should include pregnancy status assessment until pregnancy outcome is known.

Please note that pregnancy in and of itself is not an AE or an SAE. Pregnancy should not be entered into the eCRF as an AE unless the Investigator suspects an interaction between the study drug and the contraceptive method. Additionally, all information received will be assessed for any AEs and SAEs and processed per study guidelines. If the subject is discontinued because of pregnancy, pregnancy will be documented as the reason for study discontinuation. Spontaneous abortions and stillbirths will be reported as SAEs.

8.3.3. Reporting to IRBs and Regulatory Authorities

Investigators will receive initial, and follow-up expedited safety reports (ESR) (unexpected SAEs that are determined to be associated with the use of study drug) from the Sponsor or its representatives. The Investigator is responsible for fulfilling applicable local reporting requirements to their Institutional Review Board (IRB). Investigators must forward copies of the IRB notification to the Sponsor or its representatives.

In the US, the Sponsor will be responsible for notifying the FDA of any serious unexpected suspected adverse reaction that is determined to be associated with the use of study drug. The Sponsor’s assessment of attribution and expectedness will determine regulatory reporting.

8.3.4. Follow-up of Adverse Events/Serious Adverse Events

All AEs and SAEs documented at a previous visit that are designated as not recovered/resolved, will be reviewed by the Investigator at subsequent visits.

All AEs will be followed until resolution of AE, completion of the subject’s study participation, or study termination, whichever occurs first.

Serious AEs 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 drug or to factors unrelated to study conduct.
- The Investigator and Medical Monitor agree that follow-up is no longer necessary.

Follow-up reports from the Investigator must be provided via completion of the eCRF AE page and accompanying paper SAE page within 24 hours of the Investigator’s first knowledge of the new information. Additional information (i.e., hospital records, laboratory, or other diagnostic test results) should be provided if requested and/or indicated. In addition, for SAEs, the follow-up information should be added using the same form the initial SAE

was reported on. It should be completed and submitted to IQVIA Biotech Safety via email: [redacted]

Rules for AE/SAE follow up apply to all subjects, including those who withdraw consent before study completion (to the extent allowed). The Investigator will ensure that follow up includes further investigations to elucidate the nature and/or causality of the AE/SAE. These investigations must be consistent with appropriate medical management and subject consent.

Investigators are not obligated to actively seek AEs or SAEs in former study subjects that occur pursuant to the follow-up period. However, if the Investigator or designee learns of any AE or SAE at any time after a subject has been discharged from the study and the event is considered as reasonably related to the study drug, the Investigator will notify the Sponsor or its representatives.

9. STATISTICAL METHODS

Categorical variables will be summarized as the number and percentage of subjects within each category (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).

Data from all investigational sites will be pooled in the analyses.

A detailed statistical analysis plan (SAP) will be finalized before database lock and will document the analysis methods, data handling procedures, and other statistical analysis issues. Statistical analyses will be performed using SAS® software version 9.4 or higher.

9.1. Sample Size Calculation

The number of subjects planned for inclusion in this study is 43. 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. Subjects who discontinue the study before receiving the first dose of CMP-001 may be replaced to ensure at least 43 enrolled subjects.

A sample size of 43 achieves [redacted] power to detect a difference of [redacted] using normal approximation method at one-sided alpha level of 0.05, assuming that the null hypothesis for ORR is [redacted], and the alternative hypothesis for ORR is [redacted]. The sample size calculation is performed in PASS 2020 using the normal approximation to the binomial distribution.

9.2. Analysis Sets

The main analysis sets are defined in this section. Additional analysis sets may be defined in the SAP.

9.2.1. Intent-to-Treat Analysis Set

The Intent-to-Treat (ITT) Analysis Set is defined as all subjects who receive at least 1 dose of study drug. This analysis set will be the primary analysis set for all efficacy endpoints.

9.2.2. Safety Analysis Set

The Safety Analysis Set is defined as all subjects who receive at least 1 dose of study drug. This analysis set will be the primary analysis set for all safety endpoints.

9.2.3. 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 biomarker at Baseline and after CMP-001 injection.

9.2.4. Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set is defined as all subjects who receive CMP-001 and have evaluable samples at Baseline and after CMP-001 injection.

9.3. Background Characteristics

9.3.1. Disposition

The number and percentage of subjects who screen fail, enroll in the study (receive their first dose of study drug), discontinue study treatment, and who discontinue the study will be summarized. The primary reason for treatment and study discontinuation will also be summarized.

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

9.3.2. Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics (age, sex, race, ethnicity, body weight, height, and BMI) will be summarized using descriptive statistics for the ITT Analysis Set and listed by subject.

9.3.3. Eastern Cooperative Oncology Group Performance Status

ECOG data will be presented in a by-subject data listing. Change from Baseline in ECOG Performance Status will be summarized for the ITT Analysis Set.

9.3.4. Head and Neck Squamous Cell Carcinoma History

Head and neck squamous cell carcinoma history (time since diagnosis, tumor stage, nodal status, and metastatic disease status at time of diagnosis) will be summarized using descriptive statistics for the ITT Analysis Set and listed by subject. HNSCC history will be captured on a separate eCRF in the EDC system. All prior HNSCC treatments will be captured on a Prior Cancer Treatment eCRF. Prior cancer treatments will be presented in the data listings.

9.3.5. Prior Cancer Treatments

All prior treatments for HNSCC will be captured in the EDC separately from other prior medications. A summary of the number of prior lines of cancer therapy, best response on prior PD-1, and last response on prior PD-1 will be generated for the ITT Analysis Set. Prior cancer treatment details will be presented in the data listings.

9.3.6. Medical and Surgical History

Medical and surgical history will be listed by subject. Medical history will be coded using MedDRA.

9.3.7. Protocol Deviations

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

9.3.8. Prior and Concomitant Medications

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

Concomitant medications will be assessed continually from 30 days before the first dose of study drug (W1D1) through 30 days after the last dose of study drug (both CMP-001 and

pembrolizumab). Treatment medications for study-related AEs that occur more than 30 days after the last dose of study drug will be collected.

Medications will be coded using the most recent version of the World Health Organization drug dictionary and summarized according to the Anatomical Therapeutic Chemical (ATC) classes, and preferred term for each dose group for the Safety Analysis Set. Subjects will be counted only once for a given concomitant medication for each ATC class and preferred term in the summary tables.

Concomitant medications will be presented in a by-subject data listing.

9.4. Study Drug Exposure and Compliance

The number of CMP-001 and pembrolizumab doses received by each subject will be summarized descriptively for the Safety Analysis Set. The duration of each treatment, dose intensity and relative dose intensity will also be summarized.

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

Pembrolizumab dosing, including date, time, and dose administered, will be presented in a by-subject data listing.

9.5. Efficacy Analyses

9.5.1. Confirmed Objective Response Rate

The primary efficacy endpoint for the study is the confirmed ORR based on RECIST v1.1 as determined by the Investigator.

The confirmed ORR is defined as the proportion of the subjects in the analysis set who have confirmed best response as CR or PR. 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 = (cCR + cPR)/# subjects] for the ITT Analysis Set. For the ORR, 95% Clopper-Pearson confidence intervals will be calculated.

Subjects who discontinue due to death due to disease progression or disease progression, before having a post-Baseline tumor assessment will be classified as having a best response of PD. Subjects who discontinue before having a post-Baseline scan for other reasons will be counted as non-responders in the ITT analyses.

The primary efficacy analysis of confirmed ORR will be assessed according to RECIST v 1.1 by the Investigator for the ITT Analysis Set.

9.5.2. Disease Control Rate

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, CR or PR must be confirmed by a confirmatory assessment performed at least 4 weeks after the initial response. In the case of stable disease, measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

9.5.3. Duration of Response

DOR will be based on RECIST v1.1 responses as determined by the Investigator and calculated for responders in 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). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented. Censoring details will be described in the SAP, including handling of subjects who continue to be followed for PTFU disease assessments.

9.5.4. Progression-Free Survival

Progression-free survival (PFS) is defined as the time from first CMP-001 injection to disease progression or death from any cause. PFS will be calculated based on RECIST v1.1 as determined by the Investigator. Subjects who are alive and progression-free at the time of analyses will be censored in the analyses. Additional censoring rules may be defined in the SAP. Median PFS will be calculated using the Kaplan-Meier method for ITT Analysis Set. A Kaplan-Meier plot will also be generated for PFS.

An additional iPFS analysis based on Investigator assessments using iRECIST will be also be performed.

9.5.5. Overall Survival

OS will be calculated as the time from first CMP-001 injection to death due to any cause. Subjects who are alive at the time of analyses will be censored in the analyses at the time of last study contact. Median OS will be calculated using the Kaplan-Meier method for the ITT Analysis Set. A Kaplan-Meier plot will also be generated for OS.

9.5.6. Post-progression Disease Response

Post-progression disease assessments of tumor response based on iRECIST evaluated by the Investigator will be summarized in a similar way to the RECIST v1.1 assessment, and will include the calculation of iORR, iDOR, and iPFS for the ITT Analysis Set.

9.6. Safety Analyses

The assessment of safety will be based on the following assessments: AEs, clinical laboratory tests, vital sign measurements, ECGs, and physical examinations.

9.6.1. Adverse Events

TEAEs will be coded using MedDRA 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 [SOC] 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).

Additional summary tables will be generated for Grade 3 or higher TEAEs, TEAEs considered related to treatment (possibly + probably + definitely), TEAEs by maximum grade and relationship, TEAEs resulting in death, SAEs, and TEAEs leading to treatment discontinuation.

A by-subject AE data listing, including verbatim term, SOC, preferred term, treatment, grade outcome, and relationship to treatment for CMP-001 and pembrolizumab, will be generated.

Separate listings will also be generated for TEAEs ≥ Grade 3, TEAEs considered related to study treatment (possibly, probably, or definitely), TEAEs resulting in death, SAEs, and TEAEs leading to treatment discontinuation.

9.6.2. Clinical Laboratory Assessments

Safety central laboratory data 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 from Baseline tables will also be created. The categories in the shift tables will be WNL, Low, and High. WNL and Normal will be used when appropriate for urinalysis parameters. Clinically significant post-Baseline laboratory values will be reported as AEs. 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 central laboratory assessments will be presented in the data listings.

9.6.3. Vital Signs

Vital signs 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. Clinically significant post-Baseline vital sign findings will be reported as AEs. A by-subject data listing of all vital sign data will be generated.

9.6.4. Physical Examinations

Detailed information on the physical examinations will be listed by subject. Clinically significant post-Baseline physical examination findings will be reported as AEs.

9.6.5. Electrocardiograms

Heart rate, PR interval, QRS interval, QT interval, and QTcF interval 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. Clinically significant post-Baseline ECG findings will be reported as AEs. A by-subject data listing of all ECG data will be generated.

9.7. Pharmacokinetic Analyses

Blood samples obtained at predetermined time points may be analyzed for CMP-001 concentrations and metabolites for the Pharmacokinetic Analysis Set according the Schedule of Assessments (Table 1). PK parameters based on the actual sample collection times will be determined using standard noncompartmental methods. The PK parameters that may be assessed include, but are not necessarily limited to, maximum observed serum concentration (C_{max}), time of maximum observed serum concentration (t_{max}), area under the serum concentration-time curve from time zero to the last quantifiable time point ($AUC_{0\text{-}last}$), area under the serum concentration-time curve from time zero extrapolated to infinity ($AUC_{0\text{-}\infty}$), terminal elimination half-life ($t_{1/2}$).

Additional details on the PK analyses will be provided in the SAP.

9.8. Pharmacodynamic Analyses

Concentrations of CXCL10 and other chemokine or cytokine biomarkers will be summarized using descriptive statistics for all time points for the Pharmacodynamic Analysis Set.

9.9. Exploratory Tumor Biopsy Analyses

Tumor biopsy obtained at predetermined time points, according the Schedule of Assessments (Table 1), may be analyzed for protein, RNA, DNA, or other biomarkers related to TLR9, immune checkpoints, and potential markers of resistance or response to immunotherapy for the Pharmacodynamic Analysis Set.

9.10. Appropriateness of Measures

The safety assessments in this protocol (i.e., physical examination, vital signs, hematology, serum chemistry, urinalysis, coagulation, thyroid function, AEs, ECGs, and concomitant medications) are widely used and generally recognized as reliable, accurate, and relevant for an early phase oncology study. The safety assessments are adequate to protect the subjects' safety.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

10.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of the Sponsor will determine the adequacy of the facilities and discuss with the Investigator(s) and other site personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from the Sponsor or its representatives will have regular contacts with the investigational site, for the following:

- Provide information and support the Investigator(s)
- Confirm that the facilities remain acceptable
- Confirm that the study team is adhering to the protocol, data are being accurately recorded in the eCRFs, and the investigational product is being properly maintained and accountability records are current
- Perform source data verification with access to all original clinical records for each patient

Additional details regarding monitoring procedures and responsibilities are provided in the Clinical Monitoring Plan.

10.2. Case Report Forms

Electronic case report form (eCRF) will be used in this study. An eCRF is required and should be completed for each screened and enrolled subject. The completed eCRFs are the sole property of Checkmate Pharmaceuticals, Inc. and should not be made available in any form to third parties without written permission from Checkmate Pharmaceuticals, Inc. Limited data will be collected for Screen Failures.

The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the eCRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The eCRFs must be electronically signed by the Investigator to attest that the data contained on the eCRF is true. Any corrections to entries made in the source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital’s or physician’s subject chart. In these cases, data collected on the eCRFs must match the data in those charts.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Data Quality Assurance

Steps will be taken to ensure the accuracy and reliability of data. Such steps will include the selection of qualified Investigators and appropriate sites, review of protocol procedures with Investigators and associated personnel before study start, and periodic site monitoring visits by the Sponsor or its representatives. Before study initiation, Investigators and site personnel will receive specific training with regards to study procedures and systems as required. Training will include use of clinical laboratory kits and central laboratory operations.

Data management representatives will be available to provide assistance to study center personnel regarding entering subject data. The Sponsor or its representatives will review data contained within eCRFs for accuracy and completeness during remote and/or on-site monitoring visits and after entry into the database. Identified discrepancies will be queried and resolved with the Investigator (or designee) as indicated.

11.2. Quality Assurance Audits

To ensure compliance with Good Clinical Practice (GCP) and all applicable regulatory requirements, the Sponsor and/or designee may also conduct a quality assurance audit. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements.

11.3. Audits and Inspections by Regulatory Authorities

A regulatory authority or an IRB may visit the site to perform audits or inspections. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

11.4. Retention of Records

The Investigator must maintain all documentation relating to the study for a period of 2 years after a marketing application is approved for the test article, or if not approved, or if no application is to be filed, 2 years following the discontinuance of the test article for investigation [21 CFR 312.6I)]. If it becomes necessary for the Sponsor or a Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

12. ETHICS

12.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to Sponsor or its representatives before he or she can enroll any patient/subject into the study. Initial IRB approval and all materials approved by the IRB for this study, including the ICF and recruitment materials, must be maintained by the Investigator and made available for inspection.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. No changes will be made in the study without IRB approval, except when required to eliminate apparent immediate hazards to human subjects. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Sponsor or its representatives will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

Notification of the End of Clinical Trial will be sent to the IRB within 90 days after completion of follow-up for the last subject or per local regulations and guidelines.

In case the study is ended prematurely, the IRB will be notified within 15 days or per local regulations and guidelines, including the reasons for the premature termination.

The Clinical Study Report will be sent to the sites, and IRB where appropriate per local regulations and guidance, within one year after the End of Clinical Trial.

12.2. Ethical Conduct of the Study

This study will be conducted in compliance with the protocol and in accordance with current US FDA regulations. This study is also designed to comply with ICH E6 Guideline for GCP (CPMP/ICH/135/95), the European Union Clinical Trials Directive 2001/20/EC, as well as the ethical principles that have their origin in the Declaration of Helsinki, adopted by the 18th World Medical Assembly Helsinki, Finland, June 1964 and subsequent amendments.

12.3. Written Informed Consent

The ICF should be written in accordance with the current revision of the Declaration of Helsinki and current ICH and GCP guidelines. The Sponsor or its representatives will provide template ICF to the Investigator. The final ICF must be approved by the Sponsor or representatives before being reviewed and approved by the IRB. The final IRB approved ICFs must be provided to the Sponsor or its representatives for regulatory purposes.

The Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject

should be given the opportunity to ask questions and allowed time to consider the information provided.

Each subject must provide voluntary written informed consent (and sign other locally required documents) according to local requirements after the nature of the study has been fully explained. Each subject must sign an ICF before any study-related activities are performed and before participation in the study. A copy of the signed ICF must be provided to the subject, and the original signed ICF must remain in each subject's study file and must be available for verification by the study monitor at any time. The Investigator will also ensure each subject follows the proper re-consenting procedures for all applicable or additional versions of the ICF that become effective while they are enrolled in the study.

13. PUBLICATION POLICY

All information concerning CMP-001, Sponsor operations, patent application, formulas, manufacturing processes, basic scientific data, and formulation information, supplied by the Sponsor or its representatives to the Investigator and not previously published, is confidential and remains the sole property of the Sponsor. The Investigator agrees to use this information only to complete this study and not for other purposes without the Sponsor written consent.

The institution and Investigator understand that the information developed in this study will be used by the Sponsor in connection with the continued development of CMP-001, and thus may be disclosed as required to other Investigators, government regulatory agencies, or other scientific groups. To permit the information derived from this study to be used, the Investigator is obligated to provide the Sponsor with all data obtained in the study.

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15. APPENDICES

APPENDIX A. ECOG PERFORMANCE STATUS

Grade	Eastern Cooperative Oncology Group (ECOG)[a]
0	Fully active, able to carry on all predisease-performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Death

a. Oken et al 1982

APPENDIX B. APPROXIMATE MAXIMUM AMOUNT OF BLOOD DRAWN FOR 1 YEAR OF STUDY PARTICIPATION

Study Phase	**Estimated Blood Volume**
Screening/Baseline	25 mL
Weekly Dosing (2 doses every week)	50 mL
Q3 Week Visits (~16 visits over 1 year)	400 mL
End of Treatment	25 mL
Total Blood Volume Estimate for 1 year of study participation	500 mL (approximately 2 cups)

APPENDIX C. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) VERSION 5.0

Common Terminology Criteria for Adverse Events Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE version 5.0 term is a MedDRA Lowest Level Term.

Definitions

A brief definition is provided to clarify the meaning of each AE term. A single dash (-) indicates a definition is not available. Grade refers to the severity of the AE. The CTCAE displays Grade 1 to Grade 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
- **Grade 3** Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare ADL**.
- **Grade 4** Life-threatening consequences; urgent intervention indicated.
- **Grade 5** Death related to AE.

A Semi-colon indicates “or” within the description of the grade.
A single dash (-) indicates a grade is not available. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than 5options for Grade selection.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Selfcare ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

*Version 5.0 Publish date 27 November 2017 (v5.0: 27 November 2017)
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

APPENDIX D. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) VERSION 1.1

Response criteria were adapted from: RECIST Criteria; Version 1.1, 2009 (https://project.eortc.org/recist/wp-content/uploads/sites/4/2015/03/RECISTGuidelines.pdf) These criteria are provided as reference; any discrepancy should be resolved by consulting the original publication.

Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response, it is necessary to estimate the overall tumor burden at Baseline and use this as a comparator for subsequent measurements. Only subjects with measurable disease at Baseline should be included in protocols where objective tumor response is an endpoint. Measurable disease is defined by the presence of at least 1 measurable lesion.

A measurable lesion is defined as one that can be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 1 cm by CT scan (CT scan slice thickness no greater than 0.5 cm)
- 1 cm caliper measurement by clinical examination (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 2 cm by chest X-ray

Non-measurable lesions are defined as all other lesions, including small lesions (longest diameter < 1.0 cm or pathological lymph nodes with ≥ 10 to < 1.5 cm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability:

Bone lesions:

Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as contrast-enhanced CT or MRI can be conserved as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

Cystic lesions:

Lesions that meet the criteria for radiographically-defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions with prior local treatment:

Tumor lesions situated in a previously irradiated area, or in an area subjected to other

loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Baseline Documentation of Target and Non-Target Lesions

Baseline documentation of tumor sites may include imaging assessment of disease in the chest, abdomen, and pelvis. A Baseline CNS image is required for all subjects within 3 months of Screening. All Baseline tumor measurements must be documented within 4 weeks before start of therapy.

Target Lesions

All measurable lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at Baseline (this means in instances where subjects have only 1 or 2 organ sites involved a maximum of 2 and 4 lesions, respectively, will be recorded). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion that can be measured reproducibility should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the Baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The Baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at Baseline. Measurements are not required, and these lesions should be followed as ‘present,’ ‘absent,’ or in rare cases ‘unequivocal progression.’ In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (i.e., ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

Tumor Response Criteria

Evaluation of Target Lesions

Complete response: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 1 cm.

Partial response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the Baseline sum diameters.

Progressive disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the Baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 0.5 cm (NOTE: the appearance of 1 or more new lesions is also considered progression).

Stable disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete response: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 1 cm short axis).

Non-complete response/Non-progressive disease: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive disease: Unequivocal progression of existing non-target lesions (NOTE: the appearance of 1 or more new lesions is also considered progression).

Evaluation of Best Overall Response

The best overall response (BOR) is recorded from the start of the study treatment until the End of Clinical Trial, taking into account any requirement for confirmation. The subject's BOR assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. In non-randomized studies where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'BOR.'

Determination of Tumor Response

Target Lesions	Non-Target Lesions	New Lesions	Response Assessment
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not Evaluated	No	PR
PR	Non-PD or Not All Evaluated	No	PR
SD	Non-PD or Not All Evaluated	No	SD
Not All Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

NOTE: Subjects with a global deterioration of health status, requiring discontinuation of treatment without objective evidence of disease progression at that time, should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of treatment. Conditions that may define "early progression, early death, and inevaluability" are study-specific and should be clearly defined in each protocol (depending on treatment duration and treatment periodicity). In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspiration/biopsy) before confirming the CR status.

Best Overall Response When Confirmation of CR or PR Are Required

When confirmation of response is required, CRs or PRs may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later).

Confirmation of CR and PR

Overall Response First Time Point	Overall Response Subsequent Time Point	BOR
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

Abbreviations: BOR = best overall response; CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

a. If a CR is truly met at the first time point, any disease seen at a subsequent time point, even disease meeting PR criteria relative to Baseline, makes the disease PD at that time point (because disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, "CR" may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response PR.

Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation using a ruler or calipers. All Baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of treatment.

NOTE: Tumor lesions in a previously irradiated area are not optimally considered measurable disease. If the Investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at Baseline and during follow-up. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

Clinical lesions will only be considered measurable when they are superficial and 1 cm diameter as assessed using calipers (i.e., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

For chest lesions, chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new

lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

Cross-sectional imaging: Computed tomography is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 0.5 cm or less. When CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (i.e., for body scans).

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by contrast-enhanced CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest sum on study (if the Baseline sum is the smallest, this is the reference for calculation of PD).

Time to Disease Progression

Defined as the time from the date of first day of enrollment to progression, as assessed by the conventional response criteria, death, or the start of further antitumor therapy. Subjects lost to follow-up will be censored at their last known alive date.

APPENDIX E. IMMUNOTHERAPY RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (IRECIST)

Response criteria were adapted from: Response Evaluation Criteria in Solid Tumors (RECIST) for use in trials testing immunotherapeutics; published in final edited form as: Lancet Oncol. 2017 March; 18(3): e143–e152. doi:10.1016/S1470-2045(17)30074-8. These criteria are provided as reference; any discrepancy should be resolved by consulting the original publication.

iRECIST

The basic principles of defining tumor lesions as measurable or non-measurable and assessing tumor responses used in iRECIST remain unchanged from RECIST v1.1. The most important change is in the introduction of an additional follow-up to confirm or withdraw an 'unconfirmed' tumor progression after initial increase in size. Similar to RECIST v1.1, iRECIST is primarily based on the use of contrast-enhanced CT and MRI, while inclusion of clinically visible superficial lesions in malignant melanoma is possible as well.

Baseline Evaluation

At Baseline, iRECIST is used similarly to RECIST v1.1 to determine the total tumor burden by defining target and non-target lesions. For that purpose, a distinction is made between measurable and non-measurable lesions (target lesions and non-target lesions).

Target Lesions

All measurable solid tumor manifestations with a minimum long axis diameter ≥ 10 mm (or at least double slice thickness), nodal lesions with a short axis diameter ≥ 15 mm and clinical measurements of superficially localized tumor lesions ≥ 10 mm (documented photographically using a tape measure) can be defined as target lesions.

Of these potential target lesions, analogous to RECIST v1.1, up to 5 lesions per subject can be determined within iRECIST, of which a maximum of 2 lesions per organ can be defined as target lesions. Paired organs, such as lung or kidneys, and organ systems, such as the skeletal or lymphatic systems, are understood as an organ group for which a maximum of 2 target lesions can be defined. The individual quantitative measurement results of the selected target lesions are noted and documented as a Baseline target sum. This Baseline sum diameters are used as reference to further characterize any objective tumor regression or progression in the measurable dimension of the disease.

Non-Target Lesions

Non-target lesions are lesions that may not be measured with a sufficient amount of reproducibility, e.g., solid tumor lesions < 10 mm, lymph node metastases with a short axis diameter ranging between 10 and 14 mm and tumor manifestations without clear borders like infiltrative organ metastases, lymphangitis carcinomatosa, or lesions with highly variable distribution patterns, such as malignant pleural and pericardial effusion or ascites. In addition to these non-target lesions, all other potential measurable target lesions which have not been selected for the category target lesions are also added to the non-target lesions category.

Several tumor lesions of 1 organ could be combined into 1 organ group, such as 'multiple lung metastases' or 'diffuse liver metastasis.' Non-target lesions are qualitatively documented as 'present' and do not require a specific indication of quantitative size or absolute number.

This procedure is intended to warrant complete lesion documentation in case of uncountable metastases.

Bone and Cystic Lesions

According to RECIST v1.1, there are specific recommendations regarding bone lesions, cystic lesions, and lesions previously treated with local therapy. First, osteolytic bone lesions or mixed lytic-blastic lesions with a measurable soft tissue component ≥ 10 mm could be considered as a target lesion. However, osteoblastic bone lesions represent non-target lesions. Second, cystic metastatic lesions ≥ 10 mm could be considered as target lesions. However, if noncystic target lesions are present in the same subject, these should be preferred. Finally, lesions with prior local treatment, e.g., radiation therapy or biopsy, should usually not be considered as target lesions unless there has been demonstrated clear tumor progression afterwards.

Follow-up

Regular follow-up response assessment every 6 to 12 weeks is recommended for iRECIST. During iRECIST follow-up monitoring, in line with RECIST v1.1, all target lesions defined at Baseline must be quantitatively re-measured and all non-target lesions must be qualitatively re-evaluated. The measurement of the maximum diameter of the target lesion at the new follow-up is independent of the previous direction of the measurement within the lesion or slice position, but always in identical slice orientation. In case a target lesion is reported as too small to measure but still visible, a default value of 5 mm could be used. In the rare case if a target lesion splits into 2 separate lesions, the separate measurements of the lesions should be added together for the target lesion sum. In case target lesions coalesce and are radiologically no longer separable, the maximum longest diameter for the coalesced lesion should be provided and the other lesion should be noted with 0 mm. Lymph node metastases are handled specifically. Even under a highly effective treatment, in most cases they will never fully disappear and will only shrink to their physiological size. Lymph nodes are considered as tumor-free once their short axis diameter is < 10 mm, but the measurements should be recorded in all subsequent follow-ups in order not to overstate progression in case of a minor increase in size, e.g., from 9 mm to 11 mm. This means that when lymph node metastases are target lesions, the tumor burden will mostly not become ‘zero’ even in the case of a CR. Please notice that a target lesion defined at Baseline assessment always remains a target lesion, even if it shows a size reduction to less than 10 mm. Similarly, a non-target lesion yielding a size increase of more than 10 mm at follow-up remains a non-target lesion but could qualify for ‘unequivocal progression’ in case of an overall level of substantial worsening in non-target disease.

With regards to the measurable target lesion, the proportional change of the sum of the target lesion can be calculated with the formula: Change in (%) = ([∑Follow-up - ∑Baseline/ ∑Nadir]/ ∑Baseline/ ∑Nadir) * 100. This formula takes as reference the smallest target sum in the study, the so-called Nadir, which could be the Baseline target sum if that is the smallest sum in the study.

Non-target lesions are assessed qualitatively, i.e., visually, as ‘present,’ ‘disappeared,’ or ‘unequivocal progression.’ When considering determining an ‘unequivocal progression’ of a non-target lesion, the total tumor load should always be taken into account in proportion and carefully weighed, as this would necessarily imply classification of ‘PD,’ even if all other lesions have responded strongly or even completely. In case of doubt, the responsible oncologist should be consulted.

In contrast to RECIST v1.1, where new tumor lesions are considered qualitatively and directly denote 'PD' and end of study, within iRECIST they are differentiated into new measurable and non-measurable lesions. Although new tumor lesions within iRECIST will also be classified as tumor progression, this progression initially counts as an immune unconfirmed progressive disease (iUPD), which should be re-assessed in a dedicated earlier follow-up after 4 to 8 weeks. For classification as new measurable or non-measurable tumor lesions, criteria applied are the same as for the Baseline examination with a maximum of 5 measurable new target lesions per subject and 2 per organ, respectively, which are measured as a separate group at the time of the first occurrence while the sum product of all new measurable target lesions is determined. The new non-measurable lesions are documented qualitatively, similarly to the non-target lesions at Baseline. Tumor lesions diagnosed for the first time in a previously unexamined body region are also classified as 'new lesions' in line with RECIST v1.1. The rationale behind this procedure is that the extension of imaging to a previously unexamined region, which leads to the detection of new tumor lesions, is usually triggered by the occurrence of new clinical symptoms.

In case of a new unclear lesion, e.g., because of its small size, this lesion should be preferably noted as a 'finding,' therapy should be continued, and follow-up evaluation could clarify if it represents truly new disease. If repeat examination confirms a new tumor lesion, then progression should be declared using the date of the initial scan when the lesion was first detected.

Tumor Response Criteria

The overall response according to iRECIST results from the combination of changes in target lesion and non-target lesion, as well as the possible detection and change of new measurable and non-measurable tumor lesions. The objective response in the context of immunotherapy (with the prefix 'i' for immune-related) is differentiated into:

- iCR, which describes the complete disappearance of target lesion and non-target lesion. All lymph nodes must be non-pathological in size (< 10 mm in short axis diameter).
- iPR, which occurs when the tumor load of the target lesion is reduced by ≥ 30% compared to the Baseline, or in the case of complete remission of the target lesion, when 1 or more non-target lesions can still be distinguished
- Immune stable disease (iSD), which is to be determined if the criteria of iCR or iPR are not met and no tumor progression is present

In case of a tumor progression and in order to facilitate differentiation of true tumor progression from pseudoprogression in clinically stable subjects, iRECIST proposes to determine first:

- Unconfirmed progressive disease due to an increase in the sum of all target lesions by at least 20% (but at least ≥ 5 mm) compared with the time point with the lowest target lesion sum (Nadir), or an unequivocal progression of non-target lesions, or by the occurrence of new measurable and/or non-measurable target lesions
- This initially unconfirmed tumor progression might be confirmed by a subsequent follow-up where:
    - Immune confirmed progressive disease is present if further progress of the target sum (≥ 5 mm), or any further progress of the non-target lesion,

and/or progress of the new measurable and non-measurable lesions either in number or in size (sum ≥ 5 mm)

In case of iUPD, the follow-up for re-evaluation and diagnosis of potential pseudoprogression should be carried out earlier after 4 to 8 weeks, in contrast to the regularly recommended time interval of 6 to 12 weeks. In case tumor progression is not confirmed and target lesions, non-target lesions, and new lesions remain unchanged, iUPD status should be kept and subsequent follow-up should be performed according to the regular schedule, e.g., after 8, 16, and 24 weeks. Moreover, if the tumor burden decreases more than 20%, this should be considered iSD; if it decreases more than 30%, this should be considered iPR. If tumor lesions completely disappear, there is iCR even after iUPD.

However, in iRECIST it is clearly recommended to carefully consider the continuation of immunotherapy at the first stage of iUPD. This decision should be thoroughly discussed with both subject and referring physicians and made only in case of subjective stable tumor disease or clinically suspected pseudoprogression. New lesions in a potentially curative therapy approach could be biopsied in order to enable a more reliable differentiation of rare pseudoprogression from more frequent PD and to be able to initiate an early modification of the tumor therapy before the subject may no longer tolerate it due to a physical deterioration. In the case that a biopsy is not technically feasible or only feasible with a significantly increased risk, the confirmation of the less probable delayed therapy response can be represented by a follow-up after 4 to 8 weeks in subjectively stable tumor subjects during this period.

According to RECIST v1.1, the RECIST working group did not believed that there were sufficient data available to recommend implementation of a metabolic and/or functional imaging response parameter. An exception is the use of fluorodeoxyglucose (FDG)-PET imaging as an adjunct to determination of progression if a positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT. However, the actual literature does not support the non-invasive differentiation of true progression from pseudoprogression by PET/CT.

Evaluation of Best Overall Response

For iRECIST, the BOR is the best time point response recorded from the start of immunotherapy until the end of treatment. Immune unconfirmed disease progression will not override a subsequent BOR of iSD, iPR, or iCR.

APPENDIX F. INTRATUMORAL RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (ITRECIST) VERSION 1.1

Response criteria were adapted from: itRECIST Criteria as described in Goldmacher GV, Khilnani AD, Andtbacka R, Luke RJ, F. Hodi S, et al. Response criteria for intratumoral immunotherapy in solid tumors: itRECIST. J Clin Oncol. 2020; 38:15_suppl, 3141 (Goldmacher-2020). These criteria are provided as reference; any discrepancy should be resolved by consulting the original publication.

INTRODUCTION

Intratumoral (IT) immunotherapy is approved for stage IIIB to IV melanoma and under evaluation in other malignancies with novel immune-stimulatory products. Standardized efficacy evaluation is essential for drug development. Current oncology response criteria, such as Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) and guidelines for immunotherapeutic trials (iRECIST), were designed only to assess response to systemic therapy.

RECIST is an evolving standardized framework for evaluating changes in tumor size, that is used in clinical trials to define treatment responses and disease progression. RECIST 1.1 and iRECIST are unsuitable for IT immunotherapy trials for several reasons. Because they were designed for systemic therapy, focal intervention renders treated lesions nonevaluable. RECIST 1.1 does not allow separate response assessment in injected and noninjected lesions, which is critical for IT immunotherapy trials. Moreover, there is no consensus on injected lesion assessment when lesions chosen for injection may change during treatment because of regression, loss of accessibility, or growth of other lesions. iRECIST has limited usefulness because the purpose of assessment after initial progression is solely to exclude pseudoprogression; it does not consider that the lesions selected for injection may change at progression.

Nevertheless, the experience of developing iRECIST by revising RECIST 1.1 for immunotherapy provides valuable guidance. Before the consensus effort of the RECIST Working Group, stakeholders devised divergent approaches to RECIST modification for immunotherapy, resulting in confusion and incomparability among trials. Without standardization, these issues may recur for IT therapy.

The goal of IT RECIST (itRECIST) is to create guidelines for capturing data and assessing response in IT immunotherapy trials. As with iRECIST, the standardized data collection and initial suggestions for response assessment of itRECIST will be refined based on collected data. We anticipate itRECIST will initially be used for exploratory analyses, with primary and secondary end points based on RECIST 1.1, until evidence indicates that itRECIST improves efficacy assessment.

itRECIST

itRECIST is designed to address the unique needs of IT immunotherapy trials but, where possible, aligns with RECIST 1.1 and iRECIST. It does not dictate which lesions to inject at each visit, but rather provides guidelines for assessing responses as treatment evolves. The key questions, and the approaches to answering them, are as follows:

1. What is the overall response? Overall response is determined as per RECIST 1.1 (or per iRECIST, after initial progression).
2. What is the maximal effect of IT therapy (with or without systemic therapy) on noninjected lesions? The smallest (nadir) total size of predesignated noninjected lesions is compared with pretreatment size.
3. What is the effect of therapy on injected lesions? During treatment, an iterative assessment accounts for changes in lesions selected for injection. After treatment, a combined response compares the smallest size achieved by each injected target lesion with its size before injection.

It is important to define a lexicon of precise and simple terms for these criteria; novel, nonintuitive terminology hinders understanding and adoption. Therefore, lesions are classified as injected or noninjected, and the terms *injected response* and *noninjected response* describe response in injected and noninjected lesions, respectively. The choice not to use the term *abscopal effect* was deliberate, because this implies causality: injecting lesion A causes a response in lesion B. Many IT immunotherapies are administered with systemic immunotherapies; hence, noninjected lesions may be affected by systemic therapy alone.

LESION MEASUREMENT

Lesion measurements should be performed per RECIST 1.1, with one exception. Briefly, either computed tomography (CT) or magnetic resonance imaging should be used to measure target lesions. For skin lesions, RECIST 1.1 recommends color photography documentation, including a size standard or caliper for scale.

RECIST 1.1 does not allow ultrasound for lesion measurement because of operator dependence and difficulty with standardization. However, in practice, ultrasound may be the only practical choice for some subcutaneous lesions. Therefore, itRECIST permits ultrasound measurement if no other lesions are available for quantitative assessment (Data Supplement). When feasible, the same operator should perform the ultrasound at all visits using the same equipment and acquisition parameters, capturing lesion images in a similar orientation, with anatomic landmarks to align with preceding scans. Standard RECIST 1.1 thresholds apply to consider a lesion measurable (≥ 10-mm longest diameter for extranodal lesions, ≥ 15-mm short axis for lymph nodes).

Most importantly, investigators should use the same imaging technique for a given target lesion at each assessment to evaluate changes over time. For instance, if a patient underwent CT at Baseline and ultrasound-guided IT immunotherapy for liver metastasis, response assessments should be based on repeat CT. Although pre-IT injection ultrasound assessments might yield information about the kinetics of response, ultrasound should not be used in itRECIST calculations in this specific example.

The intent with itRECIST is to capture both systemic and local effects of IT therapy. Thus, unlike in RECIST 1.1, injected lesions remain evaluable for overall response assessment even after local procedures, such as electroporation or low-dose irradiation, as long as these are integral to the IT regimen to support or enhance the injection effect. Although intralesional administration techniques and intrinsic tumor factors add variability to changes resulting from injection, no obvious adjustment to measurement methods would improve response assessment. Tumor biopsies are often performed as part of a clinical trial. Excisional biopsy

renders a lesion nonevaluable in itRECIST. Although core needle biopsy would not automatically make a lesion nonevaluable, its use is discouraged for target lesions. When feasible, biopsies should be restricted to nontarget lesions.

BASELINE DOCUMENTATION OF TUMOR BURDEN

At Baseline, lesions are classified as measurable (eligible for selection as target lesions) or nonmeasurable per RECIST 1.1 guidelines on size and reproducibility. Baseline lesions are categorized as target injected (T-I), target noninjected (T-NI), nontarget injected (NT-I), and nontarget noninjected (NT-NI) according to an algorithm (see Figure 1A as found in the primary publication Goldmacher-2020). As in RECIST 1.1, *target* refers strictly to lesions that are selected for measurement; it has no relationship to lesions selected for injection. One to 5 measurable lesions are designated as T-I and are used to evaluate the injected lesion response. One to 5 measurable lesions are designated as T-NI and remain noninjected for as long as possible to allow assessment of the maximal noninjected lesion response, as discussed in a later section. A sum of diameters (SOD; longest diameters for extranodal lesions and short axis for lymph nodes) is calculated for all target lesions combined, and separately for T-I and T-NI lesions (see Figure 1A as found in the primary publication Goldmacher-2020).

If only 1 lesion is measurable, although others are accessible for injection but not suitable for reproducible quantification, the measurable lesion should be designated as T-NI, because it may be more important to detect objective responses in noninjected lesions than in injected lesions as a means of assessing treatment efficacy. This suggestion must, of course, be considered in light of other clinically significant factors, such as whether the measurable lesion should be injected to palliate symptoms and whether the other injectable lesions offer sufficiently attractive injection targets to achieve the overall treatment goals.

RECLASSIFICATION OF LESIONS AFTER BASELINE

Injected lesions may change if those initially injected regress or become inaccessible, or if others enlarge. Nevertheless, target lesions always remain target, and nontarget lesions remain nontarget, regardless of whether they receive injections (see Figure 1B as found in the primary publication Goldmacher-2020). If initially noninjected lesions enlarge, the treating physician may decide the enlarging T-NI lesions can be controlled by injection (especially if injected lesions are regressing). Once injected, these lesions are recategorized as T-I lesions. T-NI lesions can also be injected when previously injected lesions regress or become noninjectable, particularly when initially selected T-NI lesions are not regressing (maximal noninjected effect has been achieved). NT-NI lesions may be recategorized as NT-I and injected when the original NT-I lesions can no longer be injected because of regression, inaccessibility, injection-site reaction, patient intolerance, or need for more aggressive anesthesia.

Guidelines for Prioritization of Lesion Injection for IT Therapy

Selection and prioritization of lesions for IT injection is a complex set of decisions made at each treatment visit and is ultimately based on clinical judgment. A complete description of the process is beyond the scope of this guidance, which is focused on response assessment, but a set of guiding principles follows.

The first priority is patient safety. Lesions are selected to minimize the potential for procedural complications and operational complexity. One important safety concern is

vascularity within and adjacent to a lesion. To minimize systemic administration, injection into tumor vasculature should be avoided. To minimize bleeding risk, vessels adjacent to a tumor should not be traversed, and areas of vascular encasement should be avoided in high-risk locations (e.g., inferior vena cava encasement for liver lesions, great vessel encasement for head and neck tumors).

The next priority is accessibility. Preference is given to visible cutaneous lesions, and superficial subcutaneous lesions and lymph nodes which are easily palpable. Deeper lesions, including nonpalpable lymph nodes and extranodal lesions in viscera or body cavities, are more difficult to access and typically require imaging guidance, increasing procedural complexity. Deciding to inject a lesion based on accessibility must be balanced against potential clinical benefits such as symptom relief.

At initiation of therapy, other factors guiding lesion prioritization include size and amount of viable tumor tissue. Other factors being equal, larger lesions are preferred because of the greater amount of tissue and because the likely older age of the lesion may indicate the potential to release a wider breadth of tumor-specific antigens to stimulate a broader repertoire of antigen-specific T cells. Very large lesions should be approached cautiously because of possible central necrosis, increased bleeding risk, and difficulty dispersing immunotherapeutics. Radiographically visible necrosis should be avoided, with IT therapy directed at viable portions of lesions. A larger lesion that is predominantly necrotic may have lower priority than a smaller lesion with little or no radiographic necrosis. Lesions with radiographic evidence of aggressiveness (e.g., local invasiveness) should have higher priority.

If additional lesions are injected after therapy begins, new or enlarging lesions should be given priority over lesions selected based on size or imaging features, but safety and accessibility are still paramount. These lesions contain actively dividing cells and therefore may be more responsive to injection. In addition, new or enlarging lesions may contain cancer cells that represent the vanguard of the disease as it attempts to evolve under the selective pressure of immunotherapy. These lesions could harbor new tumor antigens not strongly represented in previously injected lesions. Although some lesion types or anatomic locations may be better for stimulating systemic immune responses, evidence is insufficient to use such information for lesion prioritization. Nonetheless, data related to lesion response by disease site will inform such choices in the future.

Response Assessment Before Radiographic Progression

Overall response. The principle that target lesions remain target and that nontarget lesions remain nontarget regardless of injection status allows an overall assessment for each imaging visit similar to that for RECIST 1.1 (different only in allowing more target lesions, in injected lesions not becoming nonevaluable, and allowing ultrasound). Target lesion response, nontarget lesion response, and new lesion appearance are defined as they are for RECIST 1.1 and combined similarly to determine overall response for each visit (see Figure 2 as found in the primary publication Goldmacher-2020). The overall response should include all lesions classified as target at Baseline (SOD of T-I and T-NI combined v SOD at Baseline and at nadir) and all nontarget lesions (NT-I and NT-NI) combined (classified as absent, present, or collectively showing unequivocal progression). Of note, the rare instances of seeding along a needle track should not be reported as new lesions unless they show growth on subsequent imaging.

The role of fluorodeoxyglucose (FDG)–positron emission tomography and biopsy in assessing response must be further evaluated. Because radiographic assessment might not correlate with tissue response and loss of FDG uptake in injected lesions may represent necrosis, biopsy may provide additional information in case of doubt.

In the neoadjuvant setting, IT immunotherapy may yield pathologic complete response (pCR) rates surpassing clinical response rates (which include radiographic objective response and clinical assessment). For example, after 12 weeks of neoadjuvant talimogene laherparepvec in resectable stage IIIB to IVM1a melanoma, 3 patients achieved clinical CR and all achieved pCR. Additionally, 1 of 7 patients with clinical partial response (PR) achieved pCR, 6 of 21 patients with clinical stable disease (SD) achieved pCR, and even 2 of 35 patients with clinical progressive disease (PD) achieved pCR. Subanalysis of noninjected response may not apply in the neoadjuvant setting if only a single lesion is present initially.

Noninjected response. Noninjected response is based entirely on T-NI lesions. The SOD for these lesions at each time point is compared with those at Baseline and nadir, similar to target lesion response assessments in RECIST 1.1 (Table 8). Lesions designated T-NI at Baseline should remain noninjected for as long as possible to allow assessment of maximal systemic response to IT therapy in noninjected lesions. The treating physician may choose to inject T-NI lesions when they enlarge (systemic therapy alone is not restraining their growth) or when previously injected lesions have become noninjectable, especially if the T-NI lesions are not regressing. Once any T-NI lesion is injected, the noninjected response becomes nonevaluable.

Table 8: Response for Lesion Category

Responses	Definition
T-I lesions	
CR	All nonnodal lesions gone, nodal lesions < 10 mm
PR	≥ 30% decrease in SOD from last imaging assessment
PD	≥ 20% increase in SOD from last imaging assessment (≥ 5 mm absolute)
SD	Not enough growth for PD
	Not enough shrinkage for PR
NE	≥ 1 lesion cannot be measured
T-NI lesions	
CR	All nonnodal lesions gone, nodal lesions < 10 mm
PR	≥ 30% decrease in SOD from last imaging assessment
PD	≥ 20% increase in SOD from last imaging assessment (≥ 5 mm absolute)
SD	Not enough growth for PD
	Not enough growth for PD
NE	≥ 1 lesion cannot be measured or has been injected

Abbreviations: CR, complete response; NE, nonevaluable; PD, progressive disease; PR, partial response; SD, stable disease; SOD, sum of diameters; T-I, target injected; T-NI, target noninjected.

Overall response, however, remains evaluable because it is based on all target lesions together. As discussed below in the section on end points, the best noninjected response and maximal tumor shrinkage are determined based on assessments before injection of any T-NI lesion.

Injected response. Lesions selected for injection may change at each treatment visit, so there is no stable Baseline for comparison. Therefore, during treatment, the response assessment for injected lesions is iterative. At each assessment, the current SOD for all target lesions injected during the preceding treatment visit (whether originally classified or reclassified as T-I) should be compared with their SOD at the preceding assessment (see Figure 3 as found in the primary publication Goldmacher-2020). The injected response is based on SOD change from the previous assessment (Table 8). The decision about which lesions to inject should be made at this time, based on the guidelines for lesion prioritization outlined here. The new T-I SOD should be calculated and used as the comparator for the next assessment. After treatment discontinuation or during an interim analysis, the best response for injected lesions is determined by comparing the size of each injected lesion at its smallest with its size before first injection, as discussed in the section on end points.

Decisions at RECIST Progression

At the time of PD as defined in RECIST 1.1, clinical assessment should determine whether continued IT immunotherapy is warranted. If clinical progression is rapid, the decision may be made to discontinue study treatment. If the patient's condition is clinically stable as defined in iRECIST, it may be appropriate to continue treatment.

Continuing treatment in the setting of RECIST 1.1 PD is particularly relevant with a mixed response, when injected lesions regress or disappear but a new lesion develops or when existing noninjected lesions enlarge. In such a case, as discussed, the treating physician may reprioritize which lesions to inject, favoring new or enlarging lesions, if they are deemed safe and accessible for injection.

The challenge for IT immunotherapy assessment is not only to avoid misclassification of inflammatory reactions (pseudoprogression) as disease progression but also to account for injection of new or previously noninjected lesions. Additionally, the interval to confirmatory reassessment should allow sufficient time for IT therapy to produce an effect on these lesions; we recommend allowing 4 to 12 weeks (rather than 4 to 8 weeks per iRECIST).

Management at initial radiographic progression (overall response) depends on whether new lesions appear. For clinically stable subjects without new lesions, lesions should be injected if they are progressing or were previously injected, and consideration should be given to additional noninjected lesions according to the prioritization guidelines (see Figure 4A as found in the primary publication Goldmacher-2020).

New lesions, if present, should be categorized as new target or new nontarget lesions (per iRECIST), and the SOD of the new lesions should be calculated for future overall response assessment. If the new lesions are inaccessible, only existing lesions should continue to be injected, including those that are enlarging and those not yet injected. If the new lesions are accessible, they should be injected according to the principles previously outlined (see Figure 4B as found in the primary publication Goldmacher-2020). Again, the decision to inject should be based on prioritization rules and clinician discretion (described in Guidelines for

Prioritization of Lesion Injection for IT Therapy). Regardless of the presence or absence of new lesions, treatment should be discontinued in subjects with clinically unstable disease.

Response Assessment After RECIST Progression

Overall response for visits after RECIST progression is determined using a process similar to iRECIST, taking into account target lesions (injected and noninjected combined), nontarget lesions (injected and noninjected combined), and new lesions, to produce overall response categories that include immunotherapeutic CR, immunotherapeutic PR, immunotherapeutic SD, immune unconfirmed PD (iUPD), and immune confirmed PD (iCPD). An additional response category is described in the next section.

Injected lesion assessment after RECIST 1.1 progression uses the same iterative process as before. At each assessment, the current SOD of all target lesions injected at the previous visit (including any new lesions classified as new lesion targets and selected for injection) should be compared with the immediately preceding SOD of the same lesions. Then, based on prioritization rules and clinician discretion, the physician determines which lesions to inject at this visit, and the SOD of these is the new comparator for the next assessment.

Noninjected response after overall progression is also assessed as it was before. As long as the T-NI lesions remain noninjected, the T-NI SOD is compared with Baseline and nadir values to determine the noninjected lesion response. If any T-NI lesion must be injected (e.g., because of enlargement or because of inaccessibility of other lesions), the maximal noninjected response has been achieved and any subsequent noninjected response is considered nonevaluable.

Management and Response After Confirmed Progression

If RECIST 1.1 PD has been observed and a confirmatory scan shows confirmed PD per iRECIST, it may be appropriate to continue therapy and modify the lesions for injection. As discussed, these are typically mixed responses: injected lesions are responding, but new lesions have appeared or noninjected lesions have enlarged.

For example, if Baseline lesions are responding but a new lesion appears, this would be RECIST 1.1 PD (and iUPD by itRECIST). If the new lesion is injected and the next scan shows that this lesion, along with other injected lesions, has responded favorably but an additional new lesion has appeared, this would be considered iCPD by iRECIST, and therapy would be stopped. However, because the injected lesions are responding, the treating physician may decide (if the patient remains clinically stable) that the patient is deriving benefit from continued IT immunotherapy, inject the new lesion, and obtain another confirmatory scan (4-12 weeks later, based on clinical judgment).

We propose a novel response category to describe such situations, designated iTPD (with T representing therapy, which will continue for these subjects). This category encompasses situations in which the iRECIST response would have been iCPD (worsening of an existing cause of PD or appearance of a new cause, after an overall response of iUPD) despite the fact that the injected lesions are stable or responding, and the treating physician reprioritizes lesions for injection and continues IT immunotherapy. The response may be designated iTPD, and IT immunotherapy may continue, with imaging every 4 to 12 weeks, until any of the following occurs (at which point the response would become iCPD per itRECIST): clinical progression with worsening signs, symptoms, or performance status; physician and/or

patient decision to discontinue therapy because of intolerance; or radiographic progression, particularly in injected lesions (indicating that injection is failing to prevent growth) or physician determines another treatment is clinically indicated (e.g., a lesion is impinging on the spinal cord, necessitating urgent intervention).

APPENDIX G. CMP-001 INJECTION GUIDELINE

Syringe size is at the discretion of the Investigator or qualified designated staff for administering the CMP-001 study drug according to institutional guidelines or SOPs. Refer to the current Pharmacy Manual for additional information.

Method of CMP-001 Administration

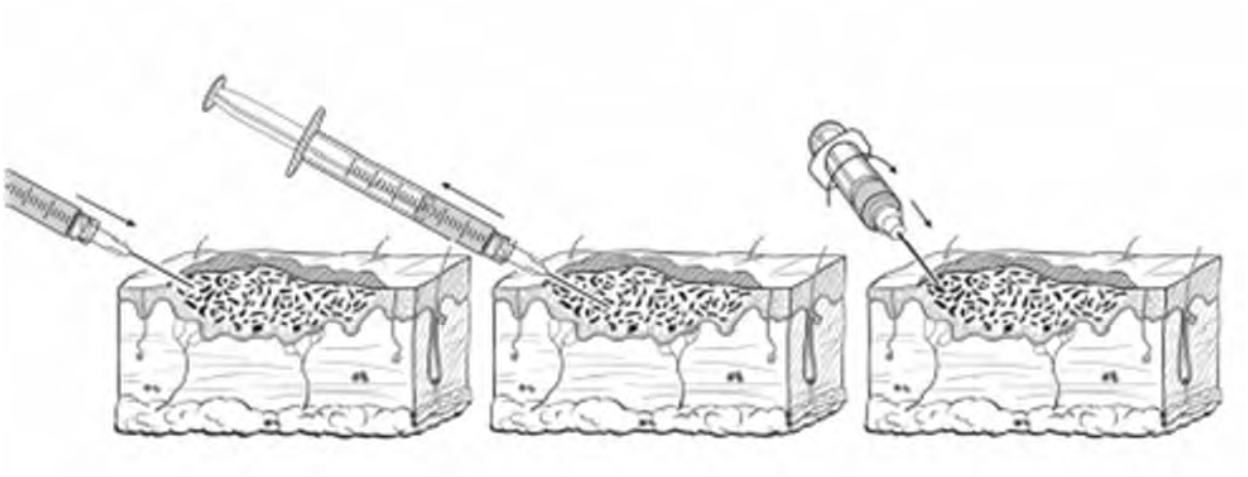
Intratumoral Injection

Using standard aseptic technique, the needle should be inserted near the tumor periphery (Figure 3 left panel) and advanced into the tumor to the desired depth while maintaining gentle backward pressure on the syringe plunger to confirm an extravascular location of the needle tip. The syringe and needle should be slowly withdrawn to within a few millimeters of the skin or tumor surface while maintaining gentle downward pressure on the plunger to inject the desired volume of CMP-001 along the needle track (Figure 3 middle panel).

Vigilance should be used when selecting lesions for injection that are in close proximity to critical structures (e.g., major airways).

With the tip of the needle still under the skin, the syringe should be rotated by ~20 º to 40º and the process of insertion and injection during needle withdrawal repeated (Figure 3 right panel). Using this process, CMP-001 is injected IT along multiple tracks through a single insertion point as far as the radial reach of the needle allows within the tumor; 2 insertion points may be used if the tumor is larger than the radial reach of the needle or the intended volume cannot be delivered through a single insertion point. If gentle injection pressure along 5 needle tracks within the tumor has not succeeded in delivering the desired volume, then the remainder of the CMP-001 may be injected peritumorally around the same lesion. If the full volume cannot be injected within the tumor, the remaining drug volume should be injected into a second accessible tumor, if present; otherwise, the remaining volume should be injected SC near an original tumor (peritumoral).

Figure 3: Method for CMP-001 Intratumoral Injection



Recommended Intratumoral Injection Volume Based on Lesion Size

Lesion Size (longest dimension)	CMP-001 Injection Volume
< 0.5 cm	Up to 0.25 mL
0.5 to 1.5 cm	Up to 0.5mL
1.5 to 2.5 cm	Up to 1 mL
> 2.5 cm	2 mL

NOTE: 2 mL is the maximum CMP-001 injection volume allowed in up to 3 accessible lesion(s) regardless of the lesion size. If the accessible lesion(s) cannot accommodate the full 2 mL volume, then the remaining volume may be injected peritumorally.

Subcutaneous Injection

Subcutaneous administration of CMP-001 should only occur when all accessible lesions have regressed. CMP-001 SC can be administered within the area of lymphatic drainage corresponding to the site of metastatic disease and follow local standards for SC injection.

In order to maximize the distribution and exposure to CMP-001, the full volume from a single dose should be distributed to as many SC sites as is practical. It is recommended that equal amounts of drug be injected at each SC site.

Preferred sites of injection include the following (see Figure 4):

- Location of the primary tumor
- Within the area of lymphatic drainage corresponding to the site of metastatic disease. For example, in a subject with a muscle or bone metastasis in the lower leg, preferred SC injection sites would be in the same leg, with the expectation that at least some of the CMP-001 will drain to lymph nodes that also contain tumor antigens. Likewise, in a subject with metastases in an upper lobe of the lung, a preferred SC injection site would be in the ipsilateral supraclavicular fossa, where the injection may activate pDC in the supraclavicular lymph nodes that also can drain the upper lung.
- Unsuitable sites for injection would include, for example, the palm of the hand or the sole of the foot.

Figure 4: Preferred Sites of Subcutaneous Injection