CMP-001-010

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

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 31 August 2020 Amendment 1 (Version 2.0) 04 February 2021 Amendment 2 (Version 3.0) 26 August 2021

INVESTIGATOR'S AGREEMENT

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

Protocol Number: CMP-001-010

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, reviewed, and approved by the Sponsor or its representatives.
- I will conduct the study in accordance with the current United States (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 (eCRF) 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: 31-Aug-2021 | 7:06 AM PDT

[redacted]

31-Aug-2021 | 7:06 AM PDT

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, 02142 United States Phone: 617-682-3625
IQVIA Biotech	Medical Monitor 24-Hour emergency contact	IQVIA Biotech Email: CMP-001-010@novellaclinical.com

Serious adverse events (SAEs) should be recorded on the SAE Report Form and completed and submitted to IQVIA Biotech Safety preferably via email to: **Safety-Inbox.Biotech@IQVIA.com** or by fax to **+1-866-761-1274** 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 that encapsulates G10, a cytosine linked to a guanine by a phosphate bond oligodeoxynucleotide
Title of Study: A multicenter, open-label, phase 2 study of intratumoral CMP-001 in combination with intravenous nivolumab in subjects with refractory unresectable or metastatic melanoma
Study Center(s): This study will be conducted at clinical sites in regions including (but not limited to) North America and Asia Pacific.
Phase of Development: Phase 2
Objectives: **Primary:** • To determine confirmed objective response with CMP-001 in combination with nivolumab in subjects with refractory unresectable or metastatic melanoma **Secondary:** • To evaluate the safety and tolerability of CMP-001 administered by intratumoral (IT) injection in combination with nivolumab in subjects with refractory unresectable or metastatic melanoma • To evaluate the efficacy of CMP-001 in combination with nivolumab in subjects with refractory unresectable or metastatic melanoma • To assess the pharmacokinetic (PK) profile of CMP-001 in combination with nivolumab in subjects with refractory unresectable or metastatic melanoma • To assess and describe the immunogenicity of CMP-001 in combination with nivolumab in subjects with refractory unresectable or metastatic melanoma **Exploratory:** • To evaluate the effect of CMP-001 in combination with nivolumab on injected and noninjected target lesions in subjects with unresectable or metastatic melanoma • To evaluate the pharmacodynamic effects of CMP-001 administered in combination with nivolumab
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 Blinded Independent Central Review (BICR) **Secondary Endpoints:** • Adverse events (AEs), serious adverse events, and AEs leading to discontinuation or death, and severity of AEs as assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0)

- Duration of response (DOR), defined as the time from date of first documented response (CR or PR) to date of documented progressive disease (PD), based on RECIST v1.1 by BICR
- Treatment response in non-injected target lesions based on RECIST v1.1 by BICR
- Progression-free survival (PFS), defined as the time from date of first dose of study treatment to date of documented PD based on RECIST v1.1 by BICR or death, whichever occurs first
- Overall survival, defined as the time from date of first dose of study treatment to date of death
- ORR, DOR, and PFS based on RECIST v1.1 and immune objective response rate (iORR), immune duration of response (iDOR), and immune progression-free survival (iPFS) based on immunotherapy Response Evaluation Criteria in Solid Tumors (iRECIST) by Investigator assessment
- Blood concentrations of CMP-001 or its metabolites
- Development of anti-Qbeta (Qb) antibodies

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 Toll-like receptor 9, immune checkpoints, and potential markers of resistance or response to immunotherapy
- Change from Baseline in blood concentrations of C-X-C motif chemokine 10 (interferon gamma-induced protein 10) and other cytokines after treatment with CMP-001

Methodology:

This is a multicenter, open-label, Phase 2 clinical study of CMP-001 administered by IT injection in combination with intravenous (IV) nivolumab in subjects with unresectable or metastatic melanoma refractory to prior programmed cell death protein 1 (PD-1) blockade.

Response and DOR will be evaluated using RECIST v1.1 criteria by BICR and Investigator assessments and using iRECIST criteria by Investigator assessment. All enrolled subjects will receive CMP-001 IT and nivolumab IV according to the treatment schedule until a reason for treatment discontinuation is reached.

Number of subjects (planned):

The number of subjects planned for this study is 100.

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. Histopathologically-confirmed diagnosis of malignant melanoma that is metastatic or unresectable at Screening.
2. Known BRAF mutation status; if BRAF V600 mutation positive, must have had prior treatment with a local Health Authority approved BRAF inhibitor, with or without mitogen-activated protein kinase inhibitor. Patients with BRAF V600 mutations who refuse a BRAF inhibitor will not be eligible.
3. Refractory to PD-1 blockade either as monotherapy or in combination with other therapies, as defined by the following criteria:
   a. Received treatment with a Food and Drug Administration approved PD-1 blocking antibody for 12 weeks or longer.
   b. Have PD (according to RECIST v1.1) within 12 weeks of the last dose of a PD-1 blocking antibody, either as monotherapy or in combination with other agents.
      – Evidence of confirmed PD must be established by Investigator assessment at least 4 weeks after the initial date of PD. The confirmatory assessment may serve as the Baseline for this study if completed within 30 days before the start of study treatment.
        NOTE: in subjects with histologically confirmed recurrence on or after adjuvant PD-1 blocking antibody, confirmatory imaging is not required.
4. Measurable disease, as defined by RECIST v1.1 and all of the following:
   a. At least 1 accessible lesion amenable to repeated IT injection.
   b. One or more measurable lesions at least 1 cm in diameter that are not intended for CMP-001 injection and can be followed as target lesions per RECIST v1.1.
   c. Documented disease progression in any lesion that was previously radiated in order to serve as a target lesion.
5. Able to provide tissue from a core or excisional/incisional biopsy (fine needle aspirate is not sufficient). A fresh tissue biopsy (within 90 days before the start of study treatment) is preferred but an archival sample is acceptable (as a substitute) if no intervening therapy was received. 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 programmed death-ligand 1 expression.
6. NOTE: for tissue sampling details, please refer to the laboratory manual.
7. Adequate organ function based on most recent laboratory values within 3 weeks before first dose of study treatment on Week 1 Day 1 (W1D1):
   a. Bone marrow function:
      – neutrophil count $\geq 1500/mm^3$
      – platelet count $\geq 100{,}000/mm^3$
      – hemoglobin concentration ≥ 9 g/dL
      – white blood cells $\geq 2000/mm^3$
   b. Liver function:

- total bilirubin ≤ 1.5 times the upper limit of normal (ULN) with the following exception: subjects with Gilbert Disease total serum bilirubin ≤ 3 times ULN
- aspartate aminotransferase and alanine aminotransferase ≤ 3 times the ULN

c. Lactate dehydrogenase ≤ 2 times the ULN

d. Renal function: estimated (Cockcroft-Gault) or measured creatinine clearance ≥ 30 mL/min.

e. Coagulation:

- International normalized ratio or prothrombin time (PT) ≤ 1.5 times ULN, unless subject is receiving anticoagulant therapy, as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants
- Activated partial thromboplastin time or 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

8. Age ≥ 18 years at time of consent.
9. Eastern Cooperative Oncology Group Performance Status of 0 to 1 at Screening.
10. Capable of understanding and complying with protocol requirements.
11. Women of childbearing potential must have negative serum pregnancy test before dosing at W1D1 and be willing to use an adequate method of contraception (Section 4.3.2.) from the time of consent until at least 150 days after last dose of study treatment.
12. 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. Uveal, acral, or mucosal melanoma.
2. Received radiation therapy (or other nonsystemic therapy) within 2 weeks before first dose of study treatment on W1D1. Subjects should have recovered (ie, Grade ≤1 or at Baseline) from radiation-related toxicities.
3. Treatment with complementary medications (eg, herbal supplements or traditional Chinese medicines) to treat the disease under study within 2 weeks before start of study treatment. Refer to Section 4.4. for prohibited therapies.
4. Received systemic pharmacologic doses of corticosteroids > 10 mg/day prednisone within 30 days before first dose of study treatment on W1D1.
   a. Subjects who are currently receiving steroids at a prednisone-equivalent dose of ≤ 10 mg/day do not need to discontinue steroids before 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.).
5. History of immune-related AE that required permanent discontinuation of PD-1 blocking antibody.

6. Not fully recovered from AEs (to Grade 1 or less [per CTCAE v5.0], with the exception of persistent adverse events or sequelae, eg, vitiligo, alopecia, hypothyroidism, diabetes mellitus, and adrenal and/or pituitary insufficiency) due to prior treatment.
   NOTE: Subjects previously treated with a CTLA-4–blocking antibody, subjects receiving corticosteroids with daily doses > 5 mg and ≤ 10 mg of prednisone equivalent for > 2 weeks, and subjects with clinical symptoms and/or laboratory findings suggesting risk for adrenal insufficiency should undergo diagnostic tests for adrenal insufficiency via local laboratory.
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, or 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, eg, 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, and 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 metastases or carcinomatous meningitis (including leptomeningeal metastases from solid tumors).
13. Prior allogenic tissue/solid organ transplant.
14. Active infection requiring systemic therapy.
15. Known or suspected active infection with severe acute respiratory syndrome coronavirus 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 first dose of study treatment on W1D1.
18. Received blood products (including platelets or red blood cells) or colony stimulating factors (including granulocyte colony stimulating factor, granulocyte/macrophage colony stimulating factor, or recombinant erythropoietin) within 30 days before the start of Screening.
19. History of permanent discontinuation of nivolumab due to infusion reactions.
20. 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 study.

21. Participation in another clinical study of an investigational anticancer therapy or device within 30 days before first dose of study treatment on W1D1.
    NOTE: Participation in the follow-up phase (receiving no study treatment) of a prior study is allowed.
22. Requires prohibited treatment (ie, non-protocol specified anticancer pharmacotherapy, surgery, or radiotherapy) for treatment of malignant tumor.
23. Has a life expectancy of less than 3 months and/or has rapidly progressing disease (eg, tumor bleeding, uncontrolled tumor pain) in the opinion of the treating Investigator.
24. Received previous CMP-001 treatment.
25. Pregnant or breastfeeding or expecting to conceive or donate eggs within the projected duration of the study, from the time of consent until at least 150 days after last dose of study treatment for women.

Investigational product, dosage, and mode of administration:

Subjects will receive CMP-001 10 mg weekly for 7 doses (W1D1 to W7D1), after which CMP-001 will be administered every 3 weeks (Q3W) (W10D1, W13D1, etc.) until the subject meets a condition for discontinuation of study treatment. 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. The initial 7 CMP-001 weekly dose schedule must be completed before starting the Q3W CMP-001 dosing schedule.

Subjects will receive nivolumab 360 mg IV over 30 minutes at W1D1 and Q3W thereafter until the subject satisfies a condition for study treatment discontinuation. Please refer to the nivolumab Investigator's Brochure. The subjects will be first dosed with CMP-001 followed by nivolumab.

Duration of treatment:

Subjects will continue study treatment until they reach a reason for treatment or study discontinuation (Section 4.5. and Section 4.6.). Subjects may continue study treatment beyond progression based upon Investigator judgment of potential benefit. Treatment will be given for a maximum of 2 years from the start of study treatment.

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

- Subject has been treated with both study treatments for at least 48 weeks
- Subject has received at least 3 doses of both study treatments beyond the date of the initial CR/iCR

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

Subjects who permanently discontinue treatment with nivolumab due to an immune related AE must also permanently discontinue treatment with CMP-001.

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

Criteria for evaluation:

Efficacy:

Disease status will be assessed by computed tomography or magnetic resonance imaging and other appropriate measures according to the Schedule of Assessments (Table 1). Calipers and photographs containing a ruler may be used to facilitate measurement of superficial cutaneous tumors. Objective responses will be assessed by a BICR and the Investigator according to RECIST v1.1. Subjects who experience PD according to RECIST v1.1 will be assessed by the Investigator according to iRECIST. Other endpoints include PFS, best overall response (BOR), and DOR.

Pharmacokinetics:

Pharmacokinetic assessment will be performed in order to assess serum CMP-001 levels following IT injection and potentially SC administration in the first 20 subjects enrolled. Samples will be collected according to the Schedule of Assessments (Table 1).

Immunogenicity:

Plasma will be obtained at time points described in the Schedule of Assessments (Table 1), for the presence of anti-Qb antibodies.

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 DNA or RNA profiling, gene expression, flow cytometry, or immunohistochemistry using tumor biopsies of injected or non-injected target lesions, collected before treatment and during 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 CTCAE v5.0
- 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:

Sample size calculation:

The study will enroll approximately 100 subjects. A subject is enrolled in the study when they have received the first dose of study treatment.

A sample size of 69 subjects achieves at least 90% power to detect a difference of 13% using a 2-sided exact test with a significance level of 0.05, assuming that the null hypothesis for ORR is 7% (Hodi-2016; Ribas-2018), and the study ORR is 20%. The sample size was increased to 100 subjects to adjust for an early discontinuation rate of 15%, and to allow for a robust assessment of safety. A sample size of 100 subjects with an ORR of 20% produces a 95% Clopper-Pearson CI for the ORR of 12.7% to 29.2% (PASS 2020).

Statistical analysis methods:

Analysis sets for safety and efficacy will include:

- Intent-to-Treat (ITT) Analysis Set: all subjects who receive at least 1 dose of study treatment
- Safety Analysis Set: all subjects who receive at least 1 dose of study treatment
- Per Protocol Analysis Set: all subjects who receive at least 1 dose of study treatment and are without major protocol deviations
- Pharmacodynamic Analysis Set: all subjects who receive at least 1 dose of CMP-001 and have at least 1 measurable sample at Baseline and at least 1 evaluable biomarker sample after CMP-001 injection
- Pharmacokinetic Analysis Set: all subjects who receive CMP-001 and have evaluable samples at Baseline and after CMP-001 injection
- Immunogenicity Analysis Set: all subjects who receive CMP-001 and have evaluable samples for immunogenicity 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, 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 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 v9.4 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 v1.1 by BICR for the ITT Analysis Set. Secondary efficacy analyses will include ORR, PFS, BOR, and DOR according to RECIST v1.1 by BICR. Additional secondary efficacy analyses will include ORR, DOR, and PFS according to RECIST v1.1, and iORR, iDOR, and iPFS according to iRECIST by Investigator assessment.

Blood concentrations of CMP-001 will be summarized using appropriate descriptive statistics by visit/time point for the PK Analysis Set.

Immunogenicity endpoints will be summarized using appropriate descriptive statistics for the Immunogenicity Analysis Set.

Table 1: Schedule of Assessments

Procedure or Assessment	Screening (Day -30 to Day -1)	W1D1	W2D1	W3D1	W4D1	W5D1	W6D1	W6D2	W7D1	Q3W (W10, W13, etc.)	End of Treatment (EOT)[a]	100-Day Follow-up (100DFU)[b]	Posttreatment Follow-up (PTFU)[c] (Q3mo)	Long-Term Survival Follow-up (LTSFU)[d] (Q3mo)
Visit Windows	**n/a**	**n/a**	**± 2d**	**± 2d**	**± 2d**	**±2d**	**±2d**	**n/a**	**±2d**	**± 3d**	**+7d**	**+7d**	**± 2weeks**	**± 4weeks**
CMP-001 Injection (Dose Number)[e]		1 SC/IT	2	3	4	5	6		7	8+				
Nivolumab Dosing (Dose Number)[f]		1			2				3	4+				
Informed Consent	X													
Eligibility Criteria Assessment	X													
Demographics	X													
Medical History	X													
Melanoma History	X													
Prior Cancer Treatment	X													
Physical Examination[g]	X	X		X					X	X	X			
Vital Signs[h]	X	X	X	X	X	X	X	X	X	X	X			
ECOG Performance Status	X	X		X					X	X	X			
Adverse Event Monitoring[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 1: Schedule of Assessments (Continued)

Procedure or Assessment	Screening (Day -30 to Day -1)	W1D1	W2D1	W3D1	W4D1	W5D1	W6D1	W6D2	W7D1	Q3W (W10, W13, etc.)	End of Treatment (EOT)[a]	100-Day Follow-up (100DFU)[b]	Posttreatment Follow-up (PTFU)[c] (Q3mo)	Long-Term Survival Follow-up (LTSFU)[d] (Q3mo)
Visit Windows	**n/a**	**n/a**	**± 2d**	**± 2d**	**± 2d**	**±2d**	**±2d**	**n/a**	**±2d**	**± 3d**	**+7d**	**+7d**	**± 2weeks**	**± 4weeks**
CMP-001 Injection (Dose Number)[e]		1 SC/IT	2	3	4	5	6		7	8+				
Nivolumab Dosing (Dose Number)[f]		1			2				3	4+				
12-Lead ECG[k]	X	X		X					X		X			
Clinical Laboratory Tests (hematology, serum chemistry, urinalysis)[l]	X	X	X	X	X	X	X		X	X	X			
Coagulation Tests[l]		X							X	X	X			
Thyroid Function Tests[l]	X			X					X	X	X			
Autoimmune Laboratory Panel[l]	X								X		X			
Pregnancy Test and Follicle Stimulating Hormone[l]	X	X			X				X	X	X			
Exploratory Biomarker Sampling[m]		X				X	X	X	X					
Pharmacokinetic Sampling[n]		X					X	X	X					

Table 1: Schedule of Assessments (Continued)

Procedure or Assessment	Screening (Day -30 to Day -1)	W1D1	W2D1	W3D1	W4D1	W5D1	W6D1	W6D2	W7D1	Q3W (W10, W13, etc.)	End of Treatment (EOT)[a]	100-Day Follow-up (100DFU)[b]	Posttreatment Follow-up (PTFU)[c] (Q3mo)	Long-Term Survival Follow-up (LTSFU)[d] (Q3mo)
Visit Windows	**n/a**	**n/a**	**± 2d**	**± 2d**	**± 2d**	**±2d**	**±2d**	**n/a**	**±2d**	**± 3d**	**+7d**	**+7d**	**± 2weeks**	**± 4weeks**
CMP-001 Injection (Dose Number)[e]		1 SC/IT	2	3	4	5	6		7	8+				
Nivolumab Dosing (Dose Number)[f]		1			2				3	4+				
Blood Sampling for Cytokine and Complement[o]		X		X			X							
Immunogenicity Sampling[p]	X								X		X		X	
Tumor Biopsy[q]	X					X								
Disease Assessment (radiographic imaging)[r]	X[s]									W13[u]; Q9W	X		X	
Disease Assessment (CNS Imaging)[r]	X[s, t]									W13[u]; Q9W	X		X	
Disease Assessment (photographic imaging)[r]	X[s]	X								W13[u]; Q9W	X		X	
100-Day Follow-up (Office or Phone Call)												X		
Long-Term Survival Follow-Up Phone Call														X

Abbreviations: 100DFU = 100-Day Follow-up; AE = adverse event; BICR = Blinded Independent Central Review; CNS = central nervous system; CRS = cytokine release syndrome; d = day; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; IT = intratumorally; LTSFU = long-term survival follow-up; MRI = magnetic resonance imaging; n/a = not applicable; PD = progressive disease; PE = physical examination; PTFU = posttreatment follow-up; Q3W = every 3 weeks; Q3mo = every 3 months; Qb = Qbeta; RECIST = Response Evaluation Criteria in Solid Tumors; SC = subcutaneously; W = week.

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 at which the Investigator decides to discontinue study treatment. If a subject has CMP-001 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.
b. The 100DFU is a safety follow-up visit that may be conducted at the study site or via phone. This visit should occur 100 days (+7) after the EOT.
   NOTE: If a subject's 100DFU, PTFU, and LTSFU visits overlap, then the visits can be combined into 1 study site visit.
c. Posttreatment follow-up will be conducted Q3mo (± 2 weeks) for all subjects who discontinue study treatment for reasons other than disease progression (either per RECIST v1.1, iRECIST, or clinical PD per Investigator) but have not met criteria for study discontinuation. These subjects should remain on study and receive disease assessments Q3mo, until discontinuation.
d. LTSFU will be conducted Q3mo (± 4 weeks) after the EOT visit or the last disease assessment date in PTFU and may occur via phone.
e. CMP-001 dosing will begin on W1D1. Weekly dosing: A window of ± 2 days is permitted for CMP-001 dosing from W1D1 to W7D1. 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. Subjects must complete all 7 weekly CMP-001 doses before moving to the Q3W dosing schedule. Q3W dosing (W10D1+): A window of ±3 days is permitted for CMP-001 dosing from W10D1 throughout the study. When nivolumab is permanently discontinued due to an immune related AE, CMP-001 must also be permanently discontinued. Refer to Section 5.3 for Treatment Compliance.
f. Nivolumab dosing will begin on W1D1 and continue Q3W throughout the study. When CMP-001 injection and nivolumab dosing fall on the same day, CMP-001 injection will be given before nivolumab dosing. Refer to Section 5.1.1 for Nivolumab 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 the W1D1, W3D1, and W7D1 CMP-001 injection visits, at every CMP-001 injection visit thereafter, 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 6 CMP-001 dosing visits (W1D1 to W6D1), vital signs must be collected before the CMP-001 injection and at 30-minute (± 15 minutes) intervals for 4 hours after CMP-001 injection. Starting at W7D1, 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 nivolumab is administered, vital signs must be collected before the start of the nivolumab infusion.
   NOTE: Oxygen saturation is not a required parameter to be collected for all subjects. Sites are to capture oxygen saturation (and FiO2, if available) at every time point only for subjects in whom an AE of hypoxia or CRS is reported.
i. AEs will be assessed continually from the time of informed consent through 100 days after the last dose of study treatment or until an alternative cancer treatment is initiated, whichever occurs first, for all subjects. Subjects who discontinue CMP-001 but remain on treatment with nivolumab will continue to have AEs collected according to this schedule until 100 days after the last dose of nivolumab.
j. Concomitant medications will be assessed continually from 30 days before the first dose of study treatment through 100 days after the last dose of study treatment or until an alternative cancer treatment is initiated, whichever occurs first. Treatment medications for study-related AEs that occur through 100 days after the last dose of study treatment will be collected during the 100DFU period.
k. 12-lead ECGs will be obtained at Screening, before the W1D1, W3D1, and W7D1 CMP-001 injections, and at EOT. Electrocardiogram parameters will include heart rate and PR interval, QRS, QT, and QT corrected intervals. Electrocardiograms 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 the CMP-001 injection. When clinical laboratory assessments are done the same day as CMP-001 injection, vital signs should be performed before collection of clinical laboratory tests. Refer to Section 7.1.12. for Clinical Laboratory Assessments.
   NOTE: For women of childbearing potential, a serum pregnancy test should be done at Screening. Serum **or** urine pregnancy tests should be done before first CMP-001 injection on W1D1, W4D1, W7D1, and Q3W thereafter and EOT. Refer to Section 7.1.13. for Pregnancy Testing. A follicle stimulating hormone 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: Screening coagulation samples (prothrombin time, international normalized ratio, and partial prothrombin time) are 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 beginning at W7D1 and continuing Q3W thereafter.
   NOTE: Free T3 and Free T4 will be drawn at each thyroid function timepoint (Screening, W3D1, W7D1, then Q3W, and at EOT).
m. Exploratory biomarker blood samples are to be collected at the following time points: W1D1 within 2 hours before CMP-001 injection; W5D1 (same day as tumor biopsy) before CMP-001 injection; W6D1 within 2 hours before CMP-001 injection, 4 hours (± 30 minutes) after CMP-001 injection, and 24 hours (± 4 hours) after CMP-001 injection (W6D2); and W7D1 within 2 hours before CMP-001 injection. Refer to Section 7.3.1. Collection of Blood for Translational Biomarker Analyses.

n. For the first 20 subjects enrolled, pharmacokinetic blood samples are to be collected at the following time points: 1) -2 to 0 hours before CMP-001 injection on W1D1, W6D1, and W7D1; 2) 4 hours (± 30 minutes) after CMP-001 injection on W1D1 and W6D1; and 3) 24 hours (± 4 hours) after CMP-001 injection on W6D2. Refer to Section 7.4. for additional details.
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, W3D1, and W6D1; 2) 4 hours (± 30 minutes) after CMP-001 injection on W1D1, W3D1, and W6D1; and 3) if any AEs of CRS are experienced.
p. Immunogenicity blood samples to assess anti-Qb antibodies are to be collected at the following time points: 1) before CMP-001 injection on W1D1 and W7D1; 2) at W58 and W103 for active subjects who are continuing study treatment or PTFU subjects who have discontinued study treatment, and at EOT.
q. Fresh tumor tissue biopsy (within 90 days before the start of study treatment) samples are preferred (an archival sample is acceptable as a substitute if no intervening therapy was received), if safe and medically feasible, at Screening and W5D1 (± 1 week) 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 programmed death-ligand 1 expression. Archival tumor biopsy samples should also be collected during Screening, if available. Refer to Section 7.3.2. for Tumor Biopsies.
r. Disease Assessment methods include radiographic (contrast-enhanced CT or MRI), photographic, 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 imaging should be performed within 30 days (+ 5 days) of W1D1.
s. To be eligible, subjects must have progressive disease according to RECIST v1.1 within 12 weeks of the last dose of a PD-1 blocking antibody (either monotherapy or combination therapy). Disease progression on PD-1 blocking antibody must be confirmed by PI assessment using baseline imaging or imaging at the time of response and 2 consecutive scans 4 weeks apart demonstrating sustained progression. The confirmatory scan may serve as the Baseline for this study if completed within 30 days before the start of study treatment. Radiographic and/or photographic imaging must be submitted for BICR eligibility verification. If available, historic photographic imaging collected at screening may be used to verify subject eligibility. Subjects must have a minimum of one target lesion not intended for IT injections identified at baseline.
t. Baseline CNS imaging by contrast-enhanced CT or MRI must be provided at Screening; on-study CNS imaging is required in presence of clinical symptoms or if CNS disease was present at Baseline.
u. Disease assessments will be performed predose beginning at W13D1 (-7 days) and repeated every 9 weeks (-7 days) (eg, W22D1, W31D1, etc.). A response (complete response, partial response, immune complete response, or immune partial response [per RECIST v1.1 or immunotherapy Response Evaluation Criteria in Solid Tumors]) 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. All scans should be performed at least 2 weeks after the most recent CMP-001 IT injection to account for injection-related pseudoprogression. Disease assessments may be performed every 12 weeks for subjects with a response continuing more than 1 year. Refer to Section 7.2. for Disease Assessments. If a CR is observed in a subject, sites should continue to obtain confirmation photographs at subsequent assessments.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibody
ADL	activities of daily living
AE	adverse event
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BICR	Blinded Independent Central Review
BMI	body mass index
BOR	best overall response
C_{avg28}	average serum concentration at Day 28
CFR	Code of Federal Regulations
cHL	classical Hodgkin lymphoma
CL_{ss}	steady-state clearance
C_{max}	maximum serum concentration
C_{min28}	trough serum concentration at Day 28
CMP-001	investigational product
CNS	central nervous system
CpG	cytosine linked to a guanine by a phosphate bond
CR	complete response
CRA	Clinical Research Associate
CRC	colorectal cancer
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CV	coefficient of variation
CXCL	C-X-C motif chemokine
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
ER	exposure-response

Abbreviation or Specialist Term	Explanation
EU	European Union
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
GCP	Good Clinical Practice
HCC	hepatocellular carcinoma
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
iCR	immune complete response
ID	identification
iDOR	immune duration of response
IEC	Independent Ethics Committee
IFN	interferon
INR	international normalized ratio
iORR	immune objective response rate
iPFS	immune progression-free survival
iPR	immune partial response
IRB	Institutional Review Board
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
MEK	mitogen-activated protein/extracellular signal-regulated kinase
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
ODN	oligodeoxynucleotide
ORR	objective response rate
OS	overall survival
pCR	pathological complete response
PD	progressive disease

Abbreviation or Specialist Term	Explanation
pDC	plasmacytoid dendritic cell
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
pMR	pathological major response
PPK	population pharmacokinetics
pPR	pathological partial response
PR	partial response
PT	prothrombin time
PTFU	posttreatment follow-up
PTT	partial thromboplastin time
Q3W	every 3 weeks
Qb	Qbeta
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RVT	residual viable tumor
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SOP	standard operating procedure
TB	total bilirubin
TEAE	treatment-emergent adverse event
TLR9	Toll-like receptor 9
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
VLP	virus-like particle
W	week
W1D1	Week 1 Day 1
WNL	within normal limits
WOCBP	woman of childbearing potential

1. INTRODUCTION

1.1. Background

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

There are several preferred Category 1 regimens (based upon high-level evidence and National Comprehensive Cancer Network consensus) available for the first-line treatment of patients with unresectable or metastatic melanoma, including PD-1 blockade monotherapy or, if a BRAF V600-activating mutation is present, a combination of agents targeted at BRAF and mitogen-activated protein/extracellular signal-regulated kinase (MEK) (NCCN-2020). In certain circumstances, nivolumab combined with ipilimumab may be another option. There are no Category 1 options for subsequent therapy once disease progression occurs on a preferred regimen (NCCN-2020). Treatments that may be considered after disease progression due to PD-1 blockade include ipilimumab or chemotherapy; however, response rates are low and both are accompanied by greater toxicity than PD-1 blocking antibody administration (Ribas-2015; Robert-2015; da Silva -2020; Davar -2015).

Some patients treated with PD-1 blockade achieve a complete response (CR) or partial response (PR) with continued treatment beyond Response Evaluation Criteria in Solid Tumors (RECIST) progressive disease (PD); however, the frequency is very low. Hodi-2016 evaluated the relationship between overall survival (OS) and response using RECIST and immunotherapy Response Evaluation Criteria in Solid Tumors (iRECIST) in patients with advanced melanoma previously treated with pembrolizumab. Of the 327 subjects who had at least 28 weeks of imaging follow-up, 24 (7%) had PD by RECIST that was not confirmed on subsequent assessment by iRECIST. Of these subjects with pseudoprogression, 13 subjects went on to achieve a CR or PR. Ribas-2018 recommended that single arm studies in the setting of continued PD-1 blockade beyond PD should rule out a null hypothesis of 6% to 7%. Given that a minority of patients achieve an objective response with initial nivolumab or pembrolizumab treatment, and there are limited treatment options post-PD-1 blockade, there is significant unmet medical need for the treatment of patients with melanoma who do not respond or who progress following treatment with PD-1 blockade.

This unmet need is even more compelling in patients with confirmed progressive disease to PD-1 blockade. The Society for the Immunotherapy of Cancer convened an Immunotherapy Resistance Task Force to provide expert guidance on the selection of patients for clinical trials with a scientific objective to address resistance to PD-1 blockade (Kluger-2020). Key elements of the guidance from this group focused on the need to ensure adequate exposure to PD-1 blockade (minimum of 6 weeks in the case of primary resistance) and to confirm progressive disease with two assessments at least 4 weeks apart, unless disease recurrence occurred during adjuvant therapy. This guidance provides the foundation for the intended patient population in this clinical trial.

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 (Qb). G10 is an ODN that contains CpG and also contains poly-G tails that allow it to form G-quadruplexes. Once administered to a patient, an antidrug antibody response to the VLP (anti-Qb antibodies) develops. Antibody-coated QbG10 is taken up by cells through Fc receptors into the endosome. In plasmacytoid dendritic cells (pDCs), antibody-coated QbG10 is taken up via FcgRII into endosomes where the G10 is released and activates TLR9 (Lemke-Miltner-2020).

Toll-like receptor 9 is found in pDCs and B cells, but Type A CpG compounds have little effect on B cells. Plasmacytoid dendritic cells 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 patients with cancer (Lombardi-2015; Demoulin-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 (CXCL)9 and CXCL10 (Swiecki-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 capable of circulating throughout the body and attacking distant tumor cells. Therefore, administration of CMP-001 intratumorally (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

The safety and efficacy data demonstrating the clinical benefit of CMP-001 IT in combination with pembrolizumab intravenous (IV) in patients with melanoma refractory to PD-1 blockade were obtained in an ongoing clinical study, Study CMP-001-001 (Milhem - 2020). In the 98 subjects treated with pembrolizumab according to the KEYTRUDA® (pembrolizumab) United States Prescribing Information (KEYTRUDA® USPI) in combination with CMP-001 10 mg IT every week for 7 weeks and every 3 weeks (Q3W) thereafter, the objective response rate (ORR) was 27.6% (27/98; 95% confidence interval [CI], 19.0%, 37.6%), including patients with responses after initial progressive disease and the best ORR by RECIST v1.1 was 23.5% (23/98; 95% CI, 15.5%, 33.1%), including 7 complete responses and 16 partial responses. This ORR is substantially higher than the 7.7% response rate observed in the 6 of 78 patients who received treatment beyond progression with pembrolizumab in the Keynote-002 study (Ahmed-2020). The clinical benefit of this combination treatment includes durable CRs and PRs in injected and non-injected target lesions and non-target lesions of the skin, lymph nodes, and viscera. The Kaplan-Meier estimate for median duration of response (DOR) for both RECIST v1.1 responders and RECIST v1.1 responders plus post-progressive disease responders was 19.9 months (95% CI, 6 months, 19.9 months). Most treatment related adverse events (TRAEs) were Grade 1 or 2 and included flu-like symptoms, including chills, fever, fatigue, nausea, vomiting, and headache, and injection site pain. The most common treatment-related Grade 3 or 4 adverse events were hypotension (6.3%) and hypertension (5.0%). No Grade 5 treatment-related adverse events were reported. Additional information is provided in the CMP-001 Investigator's Brochure (IB).

Preliminary safety and efficacy data from an ongoing Phase 2 Investigator Sponsored Trial of CMP-001 IT in combination with nivolumab in subjects with high-risk resectable melanoma (Study HCC 17-169) demonstrated clinical activity and a tolerable safety profile (Davar - 2020). Pathological responses, defined as ≤ 50% residual viable tumor (RVT), were reported in 70% of subjects (21/30) and included pathological complete response (pCR), defined as 0% RVT, in 50% (15/30) of subjects, pathological major response (pMR), defined as 1% to 10% RVT, in 10% (3/30) of subjects, and pathological partial response (pPR), defined as 11% to 50% RVT, in 10% (3/30) of subjects. In the 31 subjects evaluable for safety, CMP-001 in combination with nivolumab was generally well tolerated with an acute toxicity profile consisting predominantly of Grade 1 or 2 TRAEs. The only treatment-related Grade 3 adverse event in more than 1 subject was hypertension (n = 3, 9.7%). No Grade 4/5 TRAEs were reported. There were no dose limiting toxicities or delays in surgery related to neoadjuvant treatment. One-year recurrence free survival was 89% in patients with major pathological response (pCR and pMR) and 90% in patients with any pathological response (pCR, pMR, and pPR).

1.3. Nivolumab

1.3.1. Nivolumab Mechanism of Action

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (HuMAb; immunoglobulin G4-S228P) that targets the PD-1 cluster of differentiation 279 cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes (Schadendorf-2017). Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

Nivolumab is approved for the treatment of several types of cancer in multiple regions including the US (Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

1.3.2. Nivolumab Clinical Activity

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy in several tumor types, including non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma (RCC), classical Hodgkin lymphoma (cHL), small cell lung cancer, gastric cancer, squamous cell carcinoma of the head and neck (SCCHN), urothelial cancer, hepatocellular carcinoma (HCC), and colorectal cancer (CRC). In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in patients with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or SCCHN. Details of the clinical activity in these various malignancies are provided in the nivolumab Investigator's Brochure.

1.3.3. Benefit/Risk Assessment

Extensive details on the safety profile of nivolumab are available in the nivolumab Investigator's Brochure and will not be repeated herein.

Overall, the safety profile of nivolumab monotherapy is manageable and generally consistent across completed and ongoing clinical trials with no maximum tolerated dose reached at any

dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

A pattern of immune-related AEs has been defined, for which management algorithms have been developed; these are provided in Appendix H. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab Investigator's Brochure.

1.4. Study Rationale

1.4.1. Rationale for Combining a TLR9 Agonist with a PD-1 Blocking Antibody

PD-1 blockade is an effective and important therapy for the treatment of melanoma; however, more than 60% 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-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 studies, TLR9 agonism resulted in strong induction of cytotoxic T lymphocyte responses; however, very few objective responses were observed and the T cell responses were not sustained, especially within tumors (Appay-2006). This may be because TLR9-mediated T cell activation induces PD-1 expression on activated T cells (Fourcade-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 of melanoma to PD-1 blockade.

The ex-vivo addition of an anti-PD-1 antibody to $CD8^+$ T cells from melanoma subjects who had been treated with a TLR9 agonist significantly increased the T cell function for cytokine secretion (Fourcade-2014), providing a rationale for the use of the combination of TLR9 agonists and anti-PD-1 antibodies in cancer therapy.

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-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-2013). Mechanistic studies in the PD-L1 resistant mouse tumor models including CT26 and MCA38 colon carcinoma and TS/A 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-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-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.

1.4.2. 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.

Intratumoral 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 in distant metastases (Heckelsmiller-2002; Shirota-2012).

1.4.3. Rationale for CMP-001 Dose and Schedule

In the Phase 1b clinical study, CMP-001-001, CMP-001 IT was evaluated at doses of 1 to 10 mg using 2 dosing schedules and with preparations containing 2 different concentrations of the excipient polysorbate 20 (0.01% and 0.00167%) in combination with pembrolizumab IV in subjects with PD-1 refractory melanoma. The safety profile was similar and manageable across the CMP-001 doses of 1 to 10 mg. Antitumor activity, including durable CRs and PRs, with a predictable/manageable safety profile was observed in 23% of subjects who initiated treatment with the proposed dose and schedule for this study: CMP-001 10 mg (polysorbate 20 0.01%) IT QW for 7 doses, followed by administration Q3W in combination with pembrolizumab 200 mg IV Q3W. This dose and schedule were selected for further development. Further details can be found in the IB for CMP-001.

1.4.4. Rationale for Nivolumab Dose and Schedule

The rationale for administering nivolumab Q3W is to align with the schedule of CMP-001 evaluated in Study CMP-001-001. Population pharmacokinetic (PK) analyses have shown that the PK of nivolumab is linear with proportional exposures over a dose range of 0.1 to 10 mg/kg. The benefit-risk profiles of nivolumab 240 mg Q2W, 360 mg Q3W and 480 mg Q4W are predicted to be comparable to 3 mg/kg Q2W. This is further discussed in Section 5.1.1.1.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

- The primary objective of the study is to determine confirmed objective response with CMP-001 in combination with nivolumab in subjects with refractory unresectable or metastatic melanoma.

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 nivolumab in subjects with refractory unresectable or metastatic melanoma
- Evaluate the efficacy of CMP-001 in combination with nivolumab in subjects with refractory unresectable or metastatic melanoma
- Assess the PK profile of CMP-001 in combination with nivolumab in subjects with refractory unresectable or metastatic melanoma
- Assess and describe the immunogenicity of CMP-001 in combination with nivolumab in subjects with refractory unresectable or metastatic melanoma

2.1.3. Exploratory Objective

The exploratory objective of the study is to:

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

2.2. Study Endpoints

2.2.1. Primary Endpoint

The primary endpoint of the study is the ORR, defined as the proportion of subjects with a confirmed objective response of CR or PR based on RECIST v1.1 as determined by Blinded Independent Central Review (BICR).

2.2.2. Secondary Endpoints

The secondary endpoints of the study are:

- AEs, serious adverse events (SAEs), and AEs leading to discontinuation or death, and severity of AEs as assessed by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0)
- Duration of response, defined as the time from date of first documented response (CR or PR) to date of documented PD, based on RECIST v1.1 by BICR
- Treatment response in non-injected target lesions based on RECIST v1.1 by BICR

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

2.2.3. Exploratory Endpoints

The exploratory endpoints of the study are:

- Response in injected and noninjected target lesions per intratumoral Response Evaluation Criteria in Solid Tumors (itRECIST, Appendix F, Goldmacher-2020) by Investigator assessment
- Baseline, and change from Baseline, in tumor or blood measurements of biomarkers related to TLR9, immune checkpoints, and potential markers of resistance or response to immunotherapy
- Change from Baseline in blood concentrations of CXCL10 (interferon gamma-induced protein 10) and other cytokines after treatment with CMP-001

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a multicenter, open-label, Phase 2 clinical study of CMP-001 IT in combination with nivolumab IV in subjects with unresectable or metastatic melanoma refractory to PD-1 blockade. Eligible subjects must have confirmed disease progression during or within 12 weeks of their last dose of therapy containing a PD-1 blocking antibody for the treatment of unresectable cutaneous melanoma before enrollment. All subjects will receive CMP-001 IT and nivolumab IV according to the Schedule of Assessments (Table 1) until a reason for treatment discontinuation is reached.

Tumor tissue collection will be obtained as per instructions in the laboratory manual.

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

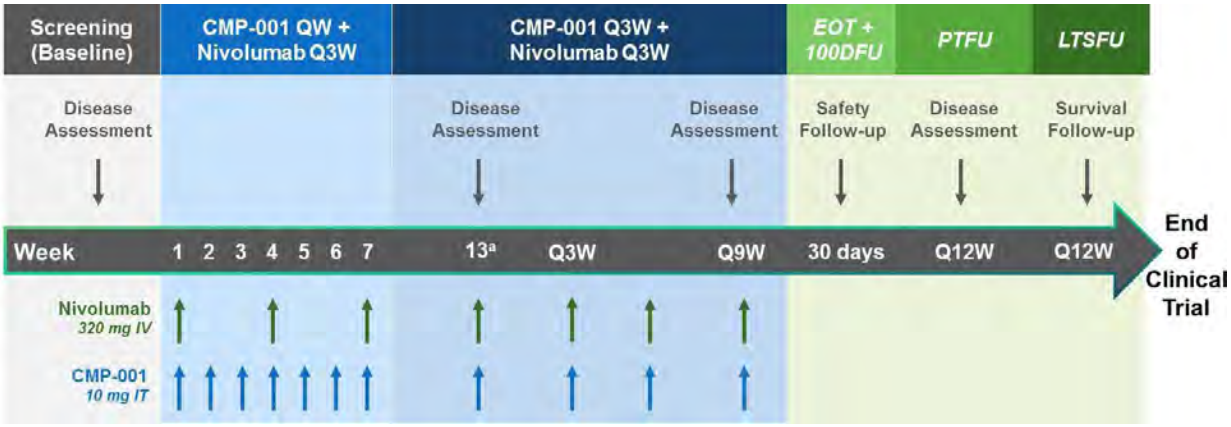
If all injectable tumors regress, CMP-001 may be injected SC in the region of prior tumors or draining lymph node bed, at the Investigator's discretion (see Appendix G). On visits where both study treatments are administered, CMP-001 IT should be administered before nivolumab. CMP-001 should be administered until a reason for treatment discontinuation is reached. See Section 5.1.3. for treatment modifications for CMP-001.

Objective responses will be assessed by BICR and Investigator assessment according to RECIST v1.1. Subjects who experience PD according to RECIST v1.1 may continue study treatment at the discretion of the Investigator and will be evaluated by the Investigator according to iRECIST. Disease status will be assessed by computed tomography (CT) or magnetic resonance imaging (MRI) and other appropriate measures beginning predose at Week 13 Day 1 (W13D1) and will be repeated every 9 weeks (eg, W22D1). Responses (CR, PR, immune complete response [iCR], or immune partial response [iPR]) will be confirmed by a follow-up disease assessment performed at least 4 weeks after the initial response date, and at least 2 weeks after the last CMP-001 injection. Disease assessments will continue every 9 weeks while the subject is on treatment. Disease assessments may continue every 12 weeks for subjects with a response lasting more than 1 year. All scans should be performed at least 2 weeks after the most recent CMP-001 IT injection to account for injection-related pseudoprogression. Imaging should not be delayed in cases where treatment is delayed.

Subjects who discontinue study treatment should complete an end of treatment (EOT) visit and 100-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).

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

Figure 1: CMP-001-010 Study Schema



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

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

3.2. Duration of Treatment with Nivolumab

The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical trials across different tumors types in the nivolumab and ipilimumab development program indicate that most of the responses occur early, with a median time to response of 2 to 4 months, and emerging data suggest that benefit can be maintained in the absence of continued treatment. A retrospective pooled analysis of 2 melanoma studies suggest the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment (Schadendorf-2017). Furthermore, a limited duration of ipilimumab, including only 4 induction doses, resulted in long-term survival in patients with metastatic melanoma, with a sustained plateau in survival starting around 2 years after the start of treatment (Schadendorf-2015).

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long-term benefit. CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumors (including 129 subjects with NSCLC), specified a maximum treatment duration of 2 years. Among 16 subjects with NSCLC who discontinued nivolumab after completing 2 years of treatment, 12 subjects were alive > 5 years and remained progression-free without any subsequent therapy. In the CA209003 NSCLC cohort, the OS curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years (Brahmer-2017). These survival outcomes are similar to phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2-year OS rates of 23% and 29%, and 3-year OS rates of 16%-18% for squamous and non-squamous NSCLC respectively) (Felip-2017).

Taken together, these data suggest that treatment beyond 2 years is unlikely to confer additional clinically meaningful benefit and that the risk of progression after discontinuing treatment at 2 years is low.

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated patients with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, patients with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment,

with the option of retreatment upon progression. Among 163 patients still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in PFS compared with those who were randomized to stop treatment, with median PFS (post-randomization) not reached vs 10.3 months, respectively; hazard ratio (HR) = 0.42 (95% CI, 0.25 to 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for patients on continued treatment to live longer (OS HR = 0.63 [95% CI, 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (ie, 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years (Spigel-2017).

Collectively, these data suggest that there is minimal if any benefit derived from continuing immuno-oncology treatment beyond 2 years in advanced tumors. Even though immunotherapy is well tolerated, patients will be at risk for additional toxicity with longer-term treatment. Therefore, in this study, treatment will be given for a maximum of 2 years from the start of study treatment.

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. Inclusion Criteria

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

1. Histopathologically-confirmed diagnosis of malignant melanoma that is metastatic or unresectable at Screening.
2. Known BRAF mutation status; if BRAF V600 mutation positive, must have had prior treatment with a local Health Authority approved BRAF inhibitor, with or without MEK inhibitor. Patients with BRAF V600 mutations who refuse a BRAF inhibitor will not be eligible.
3. Refractory to PD-1 blockade either as monotherapy or in combination with other therapies, as defined by the following criteria:
   a. Received treatment with a Food and Drug Administration approved PD-1 blocking antibody for 12 weeks or longer.
   b. Have PD (according to RECIST v1.1) within 12 weeks of the last dose of a PD-1 blocking antibody, either as monotherapy or in combination with other agents.
      – Evidence of confirmed PD must be established by Investigator assessment at least 4 weeks after the initial date of PD. The confirmatory assessment may serve as the Baseline for this study if completed within 30 days before the start of study treatment.
      NOTE: in subjects with histologically confirmed recurrence on or after adjuvant PD-1 blocking antibody, confirmatory imaging is not required.
4. Measurable disease, as defined by RECIST v1.1 and all of the following:
   a. At least 1 accessible lesion amenable to repeated IT injection.
   b. One or more measurable lesions at least 1 cm in diameter that are not intended for CMP-001 injection and can be followed as target lesions per RECIST v1.1.
   c. Documented disease progression in any lesion that was previously radiated in order to serve as a target lesion.
5. Able to provide tissue from a core or excisional/incisional biopsy (fine needle aspirate is not sufficient). A fresh tissue biopsy (within 90 days before the start of study treatment) is preferred but an archival sample is acceptable (as a substitute) if no intervening therapy was received. 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 programmed death-ligand 1 expression.
   6. NOTE: for tissue sampling details, please refer to the laboratory manual.
7. Adequate organ function based on most recent laboratory values within 3 weeks before first dose of study treatment on Week 1 Day 1 (W1D1):
   a. Bone marrow function:
      – neutrophil count $\geq 1500/mm^3$

- platelet count ≥ 100,000/mm^3
- hemoglobin concentration ≥ 9 g/dL
- white blood cells ≥ 2000/mm^3

b. Liver function:

- total bilirubin ≤ 1.5 times the upper limit of normal (ULN) with the following exception: subjects with Gilbert Disease total serum bilirubin ≤ 3 times ULN
- aspartate aminotransferase and alanine aminotransferase ≤ 3 times the ULN

c. Lactate dehydrogenase ≤ 2 times the ULN

d. Renal function: estimated (Cockcroft-Gault) or measured creatinine clearance ≥ 30 mL/min.

e. Coagulation:

- International normalized ratio or prothrombin time (PT) ≤ 1.5 times ULN, unless subject is receiving anticoagulant therapy, as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants
- Activated partial thromboplastin time or 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

8. Age ≥ 18 years at time of consent.
9. Eastern Cooperative Oncology Group Performance Status of 0 to 1 at Screening.
10. Capable of understanding and complying with protocol requirements.
11. Women of childbearing potential must have negative serum pregnancy test before dosing at W1D1 and be willing to use an adequate method of contraception (Section 4.3.2.) from the time of consent until at least 150 days after last dose of study treatment.
12. 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. Exclusion Criteria

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

1. Uveal, acral, or mucosal melanoma.
2. Received radiation therapy (or other nonsystemic therapy) within 2 weeks before first dose of study treatment on W1D1. Subjects should have recovered (ie, Grade ≤1 or at Baseline) from radiation-related toxicities.
3. Treatment with complementary medications (eg, herbal supplements or traditional Chinese medicines) to treat the disease under study within 2 weeks before start of study treatment. Refer to Section 4.4. for prohibited therapies.
4. Received systemic pharmacologic doses of corticosteroids > 10 mg/day prednisone within 30 days before first dose of study treatment on W1D1.

a. Subjects who are currently receiving steroids at a prednisone-equivalent dose of ≤ 10 mg/day do not need to discontinue steroids before 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.).

5. History of immune-related AE that required permanent discontinuation of PD-1 blocking antibody.

6. Not fully recovered from AEs (to Grade 1 or less [per CTCAE v5.0], with the exception of persistent adverse events or sequelae, eg, vitiligo, alopecia, hypothyroidism, diabetes mellitus, and adrenal and/or pituitary insufficiency) due to prior treatment.
NOTE: Subjects previously treated with a CTLA-4–blocking antibody, subjects receiving corticosteroids with daily doses > 5 mg and ≤ 10 mg of prednisone equivalent for > 2 weeks, and subjects with clinical symptoms and/or laboratory findings suggesting risk for adrenal insufficiency should undergo diagnostic tests for adrenal insufficiency via local laboratory.

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, or 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, eg, 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, and 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 metastases or carcinomatous meningitis (including leptomeningeal metastases from solid tumors).

13. Prior allogenic tissue/solid organ transplant.

14. Active infection requiring systemic therapy.

15. Known or suspected active infection with severe acute respiratory syndrome coronavirus 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 first dose of study treatment on W1D1.

18. Received blood products (including platelets or red blood cells) or colony stimulating factors (including granulocyte colony stimulating factor, granulocyte/macrophage colony stimulating factor, or recombinant erythropoietin) within 30 days before the start of Screening.
19. History of permanent discontinuation of nivolumab due to infusion reactions.
20. 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 study.
21. Participation in another clinical study of an investigational anticancer therapy or device within 30 days before first dose of study treatment on W1D1.
    NOTE: Participation in the follow-up phase (receiving no study treatment) of a prior study is allowed.
22. Requires prohibited treatment (ie, non-protocol specified anticancer pharmacotherapy, surgery, or radiotherapy) for treatment of malignant tumor.
23. Has a life expectancy of less than 3 months and/or has rapidly progressing disease (eg, tumor bleeding, uncontrolled tumor pain) in the opinion of the treating Investigator.
24. Received previous CMP-001 treatment.
25. Pregnant or breastfeeding or expecting to conceive or donate eggs within the projected duration of the study, from the time of consent until at least 150 days after last dose of study treatment for women.

4.3. Women of Childbearing Potential

A woman of childbearing potential (WOCBP) is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (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.

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 150 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 (ie, 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
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

4.4. Prohibited Concomitant Medications

The following medications are prohibited during the study (unless utilized to treat a drug-related AE):

- Immunosuppressive agents
- Any concurrent systemic anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents for treatment of unresectable or metastatic melanoma) other than the current study treatment.
- Any non-palliative radiation therapy.
- Any complementary medications (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study.
- Any live / attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose.

- Concurrent anticancer therapy with agents other than the combination drug therapy (CMP-001 + nivolumab) 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)

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

Palliative radiotherapy or palliative surgery (ie, for pain, bleeding, spinal cord compression, brain metastasis, new or impending pathologic fracture, superior vena-cava syndrome, or obstruction) 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.

4.4.1. 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.

4.5. Treatment Discontinuation

Treatment discontinuation is defined as any subject who stops receiving study treatment and does not restart within 12 weeks. Subjects who permanently discontinue (> 12 weeks) CMP-001 or nivolumab, may not be retreated with the discontinued study treatment in this study.

Study treatment should continue until 1 of the following occurs:

- Unacceptable AE that precludes further study treatment
- 2 years of study treatment
- Progressive disease per RECIST v1.1; continuation of treatment through suspected pseudoprogression is permitted at the Investigator's discretion until confirmed PD per iRECIST
- Upon request of the Sponsor or regulatory agency
- Clinical disease progression in the opinion of the Investigator
- 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 nivolumab due to an immune related AE must also permanently discontinue treatment with CMP-001.

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 nivolumab may be discontinued at the Investigator's discretion once they meet both of the following criteria:

- Subject has been treated with both study treatments for at least 48 weeks
- Subject has received at least 3 doses of both study treatments beyond the date of the initial CR/iCR

Subjects who discontinue study treatment should complete an EOT visit and 100-day safety follow-up assessments per Table 1. Subjects who discontinue study treatment for reasons other than disease progression (either per RECIST v1.1, iRECIST, or clinical PD per Investigator) should remain on study for PTFU (Section 7.8.) and receive disease assessments according to the Schedule of Assessments (Table 1).

4.6. Study Discontinuation

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

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 is defined as the last visit for the last subject on the study.

5. TREATMENT OF SUBJECTS

5.1. Administration of Study Treatment

5.1.1. Nivolumab

Subjects will receive CMP-001 10 mg IT injection followed by nivolumab 360 mg IV at W1D1 and Q3W thereafter until the subject satisfies a condition for study treatment discontinuation. Nivolumab should be administered to the subject according to the nivolumab Investigator's Brochure. Nivolumab should be administered until the subject satisfies a condition for study treatment discontinuation (Section 4.5.). On visits where both study treatments are administered, nivolumab should be administered after CMP-001. There is no specified waiting period between the end of CMP-001 injection and the initiation of nivolumab infusion.

Participants should receive nivolumab at a dose of 360 mg as a 30-minute infusion each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

There will be no dose escalations or reductions of nivolumab allowed. Participants should be dosed in accordance with the Schedule of Assessments (Table 1).

Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 5.1.5.

Doses of study treatment(s) may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed.

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of CMP-001. If discontinuation criteria are met for CMP-001 but not for nivolumab, treatment with nivolumab may continue if CMP-001 is discontinued.

Please refer to the current nivolumab Investigator's Brochure and/or Pharmacy Manual for further details regarding storage, preparation, and administration of nivolumab.

Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

5.1.1.1. Nivolumab Dose Selection

The nivolumab dose of 360 mg Q3W was selected based on clinical data and modeling and simulation approaches using population pharmacokinetics (PPK) and exposure-response (ER) analyses of data from studies in multiple tumor types (melanoma, NSCLC, and RCC) where body weight normalized dosing (mg/kg) was used.

Nivolumab PK has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, cHL, SCCHN, CRC, and urothelial carcinoma and has been safely administered at doses up to 10 mg/kg Q2W. Nivolumab monotherapy was originally approved as a body-weight based dose of 3 mg/kg Q2W and was updated to 240 mg Q2W or 480 mg Q4W in multiple indications (nivolumab Investigator's Brochure). Nivolumab 360 mg Q3W is also under evaluation in monotherapy and in combination therapy studies. Less frequent 360 mg Q3W and 480 mg Q4W dosing regimens can reduce the burden to

patients of frequent, lengthy IV treatments and allow combination of nivolumab with other agents using alternative dosing regimens.

The benefit-risk profiles of nivolumab 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W are predicted to be comparable to 3 mg/kg Q2W. This assessment is based on a comprehensive characterization of nivolumab PK, safety, efficacy, and ER relationships across indications. Population PK analyses have shown that the PK of nivolumab is linear with proportional exposures over a dose range of 0.1 to 10 mg/kg; no clinically meaningful differences in PK across ethnicities and tumor types were observed. Using the PPK model, the exposures following administration of several dosing regimens of nivolumab administered as a flat dose were simulated, including 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W. The simulated average serum concentration at steady state following administration of nivolumab 360 mg Q3W and 480 mg Q4W are predicted to be similar to those following administration of nivolumab 240 mg Q2W and nivolumab 3 mg/kg Q2W administered to participants over a wide body weight range (34 to 180 kg) across tumor types.

Nivolumab ER relationships for efficacy and safety were evaluated for IV nivolumab administered as monotherapy at the dose range of 1 mg/kg Q2W to 10 mg/kg Q2W. Generally, a flat ER relationship was observed over this dose range in melanoma, RCC, and NSCLC subjects between nivolumab exposure and clinical endpoints such as the hazard of death, probability of overall response, AE leading to discontinuation or death, Grade 3+ AEs, and/or Grade 2+ immune-mediated AEs. Therefore, 3 mg/kg IV Q2W was approved in melanoma, RCC, NSCLC, and also studied and approved in other indications. For NSCLC, there was a trend of additional benefit (especially in ORR) at 3 mg/kg IV Q2W, when compared with 1 mg/kg IV Q2W, which had a small sample size. Therefore, a flat ER relationship could only be confirmed from 3 mg/kg IV Q2W to 10 mg/kg IV Q2W for NSCLC. Flat doses of 240 mg IV Q2W nivolumab, 360 mg IV Q3W nivolumab, and 480 mg IV Q4W nivolumab have been incorporated in monotherapy and combination oncology studies, and the 240 mg IV Q2W and 480 mg IV Q4W nivolumab dose regimens are now approved in multiple indications. Q4W dosing regimens can reduce the burden to patients of frequent, lengthy IV treatments and allow combination of nivolumab with other agents using alternative dosing regimens.

Extensive ER analyses using multiple PK measures (maximum serum concentration in Cycle 1 [C_{max1}], average serum concentration at Day 28 [C_{avg28}], and trough serum concentration at Day 28 [C_{min28}]) and efficacy and safety endpoints indicated that the efficacy of the flat-dose 480 mg IV regimen is similar to that of 3 mg/kg IV Q2W. In ER efficacy analyses for OS and ORR conducted in melanoma, RCC, and NSCLC using C_{avg28} as the driver of efficacy, probabilities of achieving a response and survival probabilities at 1 year and 2 years for 480 mg IV Q4W were similar to that of 3 mg/kg IV Q2W.

Similar analyses conducted in different tumor types using the C_{min28} as the worst-case scenario for the potential loss of efficacy also showed benefit risk profiles of 480 mg IV Q4W were comparable to 3 mg/kg IV Q2W.

5.1.1.2. Clinical Pharmacology Summary

Nivolumab PK was assessed using a PPK approach for both single-agent nivolumab and nivolumab with ipilimumab.

Nivolumab as a single agent: The PK of single-agent nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab as a 60-minute intravenous infusion every 2 or 3 weeks. Nivolumab clearance

decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of 24.5% (47.6%) resulting in a geometric mean steady-state clearance (CL_{ss}) (CV%) of 8.2 mL/h (53.9%) in patients with metastatic tumors; the decrease in CL_{ss} is not considered clinically relevant. Nivolumab clearance does not decrease over time in patients with completely resected melanoma, as the geometric mean population clearance is 24% lower in this patient population compared with patients with metastatic melanoma at steady state. The geometric mean volume of distribution at steady state (CV%) is 6.8 L (27.3%), and geometric mean elimination half-life is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was 3.7-fold. The exposure to nivolumab increases dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The predicted exposure (C_{avg} and C_{max}) of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion.

Specific Populations: The PPK analysis suggested that the following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), weight (35 to 160 kg), gender, race, baseline lactate dehydrogenase, PD-L1 expression, solid tumor type, tumor size, renal impairment, and mild hepatic impairment.

Renal Impairment: The effect of renal impairment on the clearance of nivolumab was evaluated by a PPK analysis in patients with mild (eGFR 60 to 89 mL/min/1.73 m^2), moderate (eGFR 30 to 59 mL/min/1.73 m^2), or severe (eGFR 15 to 29 mL/min/1.73 m^2) renal impairment. No clinically important differences in the clearance of nivolumab were found between patients with renal impairment and patients with normal renal function.

Hepatic Impairment: The effect of hepatic impairment on the clearance of nivolumab was evaluated by PPK analyses in patients with HCC and in patients with other tumors with mild hepatic impairment (total bilirubin [TB] less than or equal to the ULN and aspartate aminotransferase (AST) greater than ULN or TB greater than 1 to 1.5 times ULN and any AST) and in HCC patients with moderate hepatic impairment (TB greater than 1.5 to 3 times ULN and any AST). No clinically important differences in the clearance of nivolumab were found between patients with mild/moderate hepatic impairment.

Details on the clinical pharmacology of nivolumab can be found in the nivolumab Investigator's Brochure.

5.1.2. CMP-001

Subjects will receive CMP-001 10 mg weekly for 7 doses (W1D1 to W7D1), after which CMP-001 will be administered by IT injection Q3W (W10D1, W13D1, 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 treatments are administered, CMP-001 should be administered before nivolumab. There is no specified waiting period between the end of CMP-001 injection and the initiation of nivolumab infusion. CMP-001 should be administered until a reason for treatment discontinuation is reached (Section 4.5.). If treatment with nivolumab is permanently discontinued due to an immune related AE, treatment with CMP-001 must be discontinued. See Section 5.1.3. 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 of the following components:

- Intravenous fluids (eg, approximately 1000 cc IV normal saline). The rate, volume, and substitution fluids are at the Investigator's discretion
- Antipyretics (eg, acetaminophen 1000 mg and a non-steroidal anti-inflammatory agent such as indomethacin 50 mg or ibuprofen 600 to 800 mg)
- Antiemetics (eg, ondansetron 8 mg)
- Antihistamine (eg, 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 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 (eg, 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 6 CMP-001 injections (W1D1 to W6D1). Beginning with the 7th CMP-001 injection (W7D1), 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. Selection of Lesion for Injection

All Screening disease assessments (radiological and photographic images) must be submitted to a BICR in order to verify disease progression. The same disease assessment method (eg, CT, MRI) used during Screening should be used throughout the study for all disease assessments, whenever possible.

Eligible subjects must have at least 1 accessible lesion amenable to repeated IT injection. Cutaneous, SC, and/or nodal tumors that are visible, palpable, or detectable by ultrasound guidance are acceptable for IT injection.

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

Tumors should be at least 0.5 cm in longest diameter and need not be the largest measurable lesion. A visceral tumor may be injected with or without the use of interventional radiology if, in the opinion of the Investigator after discussion with the Medical Monitor, it is an appropriate additional site for IT injection. The 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. 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. However, there should always be at least 1 target lesion that will not be injected for each subject. These lesions not intended for injection may be located in any metastatic site.

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).

NOTE: Subjects must have a minimum of one target lesion not intended for IT injections identified at baseline.

5.1.2.3.2. Method of CMP-001 Administration

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

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 standard operating procedures (SOPs). For methods of CMP-001 administration, see Appendix G.

5.1.3. 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 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 nivolumab dose is delayed, the CMP-001 dosing may be delayed.

5.1.4. Management of Adverse Events Associated with CMP-001

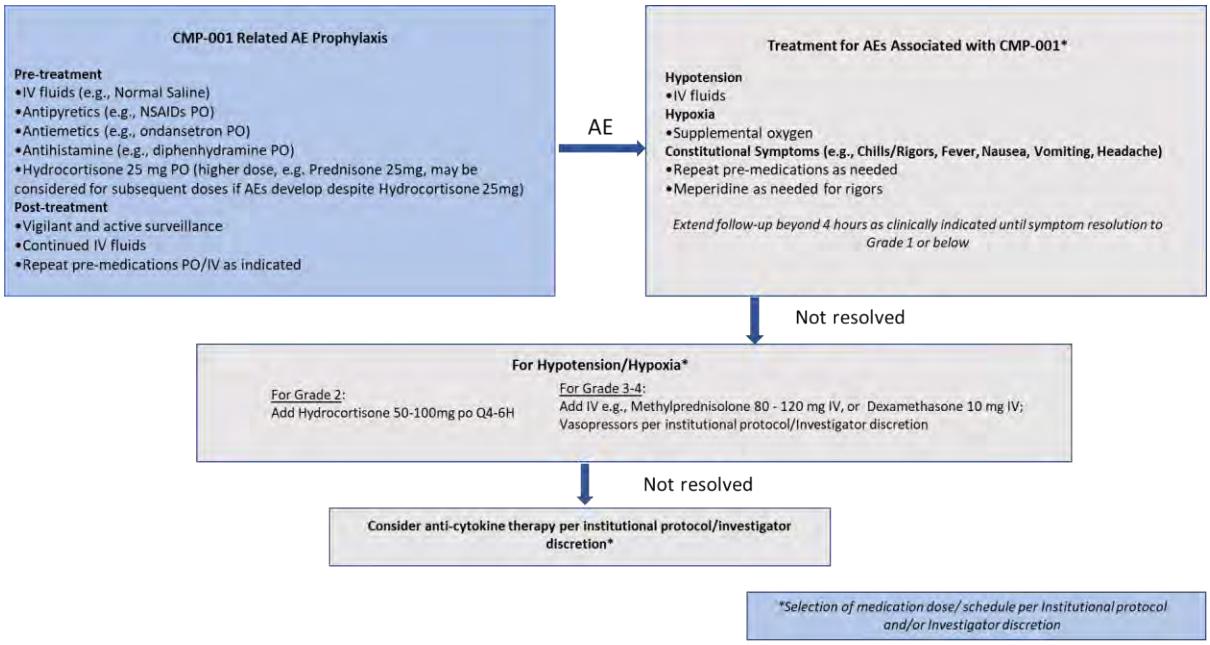
Based on observations in earlier studies, CMP-001 has been associated with AEs such as injection site reactions (see Section 5.1.4.1.), hypotension (see Section 5.1.4.3.), and flu-like symptoms. Flu-like symptoms may include fever, nausea, vomiting, chills, rigors, and/or hypotension. Additional symptoms 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 (and FiO2, if available) every time an AE of hypoxia or cytokine release syndrome (CRS) is reported for a subject.

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

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.

5.1.4.1. 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.

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.

5.1.4.2. Injection Site Reactions

Injection site inflammation is expected following the second and subsequent injections. If subjects develop 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.

5.1.4.3. Hypotension

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

5.1.4.4. 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 CRS, or any related Grade 4 AE occurs despite premedication with 25 mg prednisone or equivalent, CMP-001 should be discontinued.

5.1.5. Dose Modifications and Management of Adverse Events Associated with Nivolumab

Nivolumab has been associated with a variety of AEs. The current nivolumab Investigator's Brochure should be consulted for treatment guidance.

If a planned nivolumab dosing is delayed, the CMP-001 dosing may be delayed. When nivolumab is permanently discontinued for an immune-related AE, CMP-001 must also be permanently discontinued.

A pattern of immune-related AEs has been defined for nivolumab, for which management algorithms have been developed; these are provided in Appendix H. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Nivolumab administration should be delayed or discontinued as below:

Table 2: Dose Modifications and Management of Adverse Events Associated with Nivolumab

Drug-Related Adverse Event	Severity[a]	Action Taken	Clarifications, Exceptions, and Resume Criteria
Colitis or diarrhea	Grade 2	Delay dose[b]	Dosing may resume when AE resolves to Baseline.

Drug-Related Adverse Event	Severity[a]	Action Taken	Clarifications, Exceptions, and Resume Criteria
	Grade 3	Delay dose[b] when administered as a single agent	Dosing may resume when AE resolves to Baseline.
	Grade 4	Permanently discontinue	
Serum Creatinine Increased	Grade 2 or 3	Delay dose[b]	Dosing may resume when AE resolves to Grade ≤ 1 or Baseline value.
	Grade 4	Permanently discontinue	
Pneumonitis	Grade 2	Delay dose[b]	Dosing may resume after pneumonitis resolves to Grade ≤ 1 or Baseline value.
	Grade 3 or 4	Permanently discontinue	
Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin (TB) increased[c]	AST or ALT > 3x and ≤ 5 x upper limit of normal (ULN) or TB > 1.5 x and ≤ 3 x ULN, regardless of Baseline value	Delay dose[b]	Dosing may resume when laboratory values return to Baseline.
	AST or ALT > 5 x ULN or TB > 3 x ULN, regardless of Baseline value	Delay dose[b] or permanently discontinue (see clarification)	In most cases of AST or ALT > 5 x ULN, study treatment will be permanently discontinued. If the Investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the Investigator and the Medical Monitor/ designee must occur and approval from Medical Monitor before resuming therapy.
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Delay dose[b]	Dosing may resume after adequately controlled with hormone replacement.
	Grade 3 or 4 adrenal insufficiency or adrenal crisis	Delay dose[b] or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed before resuming therapy. If adrenal insufficiency resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.
Hyperglycemia	Grade 2 or 3 (Hyperglycemia requiring initiation	Delay dose[b]	Dosing may resume if hyperglycemia resolves to Grade ≤ 1 or Baseline value, or is

Drug-Related Adverse Event	Severity[a]	Action Taken	Clarifications, Exceptions, and Resume Criteria
	or change in daily management)		adequately controlled with glucose-controlling agents.
	Grade 4	Permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed before resuming therapy. If hyperglycemia resolves, or is adequately controlled with glucose-controlling agents, participant may not require discontinuation of study drug.
Hypophysitis/ Hypopituitarism	Symptomatic Grade 1 to 3 that is also associated with corresponding abnormal lab and/or pituitary scan	Delay dose[b]	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement.
	Grade 4	Delay dose[b] or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed before resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.
Hyperthyroidism or Hypothyroidism	Grade 2 or 3	Delay dose[b]	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement or other medical management.
	Grade 4	Delay dose[b] or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed before resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement or other medical management, participant may not require discontinuation of study drug.
Rash	Grade 2 rash covering > 30% body surface area or Grade 3 rash or suspected SJS, TEN, or DRESS	Delay dose[b]	Dosing may resume when rash reduces to ≤ 10% body surface area. Dosing may resume if SJS, TEN, or DRESS is ruled out and rash reduces to ≤ 10% body surface area.
	Grade 4 rash or confirmed SJS, TEN, or DRESS	Permanently discontinue	
Guillain-Barre Syndrome (GBS)	Any Grade	Permanently discontinue	

Drug-Related Adverse Event	Severity[a]	Action Taken	Clarifications, Exceptions, and Resume Criteria
Myasthenia Gravis (MG)	Any Grade	Permanently discontinue	
Encephalitis	Any Grade encephalitis	Delay dose[b]	After workup for differential diagnosis, (ie, infection, tumor-related), if encephalitis is not drug related, then dosing may resume when AE resolves.
	Any Grade drug-related encephalitis	Permanently discontinue	
Myelitis	Any Grade myelitis	Delay dose[b]	After workup for differential diagnosis, (ie, infection, tumor-related), if myelitis is not drug related, then dosing may resume when AE resolves.
	Any Grade drug-related myelitis	Permanently discontinue	
Neurological (other than GBS, MG, encephalitis, or myelitis)	Grade 2	Delay dose[b]	Dosing may resume when AE resolves to Baseline.
	Grade 3 or 4	Permanently discontinue	
Myocarditis	Symptoms induced from mild to moderate activity or exertion	Delay dose[b]	Dosing may resume after myocarditis has resolved.
	Severe or life threatening, with symptoms at rest or with minimal activity or exertion, and/or where intervention indicated.	Permanently discontinue	
Pancreatitis: Amylase or Lipase increased	Grade 3 with symptoms	Delay dose[b]	NOTE: Grade 3 increased amylase or lipase without signs or symptoms of pancreatitis does not require dose delay. Dosing may resume when subject becomes asymptomatic.
	Grade 4	Permanently discontinue	
Uveitis	Grade 2 uveitis	Delay dose[b]	Dosing may resume if uveitis responds to topical therapy (eye drops) and after uveitis resolves to Grade ≤ 1 or Baseline. If subject requires oral steroids for uveitis, then permanently discontinue study drug.

Drug-Related Adverse Event	**Severity[a]**	**Action Taken**	**Clarifications, Exceptions, and Resume Criteria**
	Grade 3 or 4 uveitis	Permanently discontinue	
Other drug-related AE **(not listed above)**	Grade 2 non-skin AE, except fatigue	Delay dose[b]	Dosing may resume when AE resolves to Grade ≤ 1 or Baseline value.
	Grade 3 AE - First occurrence lasting ≤ 7 days	Delay dose[b]	Dosing may resume when AE resolves to Grade ≤ 1 or Baseline value.
	Grade 3 AE- First occurrence lasting > 7 days	Permanently discontinue	
	Recurrence of Grade 3 AE of any duration	Permanently discontinue	
	Grade 4 or Life-threatening adverse reaction	Permanently discontinue	
Other drug-related laboratory abnormality **(not listed above)**	Grade 3	Delay dose[b]	Exceptions: No delay required for: Grade 3 lymphopenia Permanent Discontinuation for: Grade 3 thrombocytopenia > 7 days or associated with bleeding.
	Grade 4	Permanently discontinue	Exceptions: The following events do not require discontinuation of study drug: • Grade 4 neutropenia ≤ 7 days • Grade 4 lymphopenia or leukopenia • Grade 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to supplementation/appropriate management within 72 hours of their onset
Hypersensitivity reaction or infusion reaction (**manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions**)	Grade 3 or 4	Permanently discontinue	Refer to Section 5.1.5.2. on Treatment of Related Infusion Reactions

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; DRESS = drug reaction with eosinophilia and systemic symptoms; SJS = Stevens-Johnson syndrome; TB = total bilirubin; TEN = toxic epidermal necrolysis; ULN = upper limit of normal.

a Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0.

b Resume treatment when adverse reaction improves to Grade 0 or 1.

c Resume treatment when AST/ALT returns to Baseline.

Nivolumab dosing should also be delayed for any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, warrants delaying the dose of study medication.

Any event that leads to delay in dosing lasting > 12 weeks from the previous dose requires discontinuation, with the following exceptions:

- Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
- Dosing delays lasting > 12 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Medical Monitor (or designee).

Participants who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met (see Section 5.1.5.1.). Tumor assessments should continue as per protocol even if dosing is delayed.

5.1.5.1. Criteria to Resume Nivolumab Treatment

Please see Table 2 in Section 5.1.5. for guidance on resuming treatment.

Before re-initiating treatment in a participant with a dosing delay lasting > 12 weeks, the Medical Monitor (or designee) must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

5.1.5.2. Treatment of Nivolumab-related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study Medical Monitor/designee and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE v5.0 guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms (mild reaction; infusion interruption not indicated; intervention not indicated):

- Remain at bedside and monitor participant until recovery from symptoms. The following prophylactic premedication are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms (therapy or infusion interruption indicated but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, IV fluids]; prophylactic medications indicated for ≤ 24 hours):

- Stop the study drug infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further study medication will be administered at that visit.
- For future infusions, the following prophylactic premedication are recommended:
  - diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab and/or ipilimumab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or 4 symptoms (severe reaction, Grade 3: Prolonged [eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated):

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the Investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

5.1.5.3. Nivolumab Treatment Beyond Disease Progression

Reasons for treatment discontinuation are described in Section 4.5. These include discontinuation for progressive disease per RECIST v1.1 and clinical disease progression in the opinion of the Investigator.

However, accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD (Spigel-2017).

Participants treated with nivolumab will be permitted to continue nivolumab treatment beyond initial RECIST 1.1 defined PD, assessed by the Investigator up to a maximum of 24 months from date of first dose as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Tolerance of study treatment
- Stable performance status

5.1.6. Method of Assigning Subjects

Each subject will be assigned a unique subject identification (ID) number using an Interactive Web Response System. This number will be recorded on the subject's electronic case report form (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.

5.1.7. Blinding and Unblinding Process

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

5.2. Prior and Concomitant Medications

IMPORTANT: Please refer to Section 5.1.2.1. for required prophylaxis before CMP-001 injection. Prophylaxis administered before and after CMP-001 dosing will be collected in the electronic data capture (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 treatment (W1D1) through 100 days after the last dose of study treatment or until an alternative cancer treatment is initiated, whichever occurs first. Treatment medications for AEs related to study treatment that occur more than 100 days after the last dose of study treatment or until an alternative cancer treatment is initiated, whichever occurs first, will be collected. Subjects who discontinue CMP-001 but remain on treatment with nivolumab will continue to have concomitant medications/treatment medications collected according to 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.

5.3. 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. Nivolumab will be administered by trained site personnel at the clinic site according to the dosing instructions provided in the nivolumab Investigator's Brochure.

6. STUDY TREATMENT MATERIALS AND MANAGEMENT

6.1. Study Treatments

Nivolumab is an FDA approved drug product for the treatment of several types of cancer in multiple regions including the US (Dec-2014), the EU (Jun-2015), and Japan (Jul-2014). The physical characteristics of nivolumab are found in the nivolumab Investigator's Brochure.

CMP-001 is an investigational study drug and will be provided by the Sponsor. CMP-001 is provided as a 5 mg/mL solution in a single-use vial. Each single use vial will contain either 1 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 study drug are found in the IB and the Pharmacy Manual.

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

6.2. Study Drug Labeling and Packaging

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

- The protocol number
- The kit number
- Number of vials per kit (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 Drug Handling, Storage, Accountability

All study drug vials will be transported, received, stored, and handled in accordance with the carton and vial labels and instructions provided to the site and relevant personnel. The site's SOPs, and applicable regulations will be followed.

Appropriate storage and transportation conditions will be maintained for the study drug vials from the point of manufacture up to delivery. All shipments of study drug 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 study drug 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 study drug 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 IQVIA CRA. Such study drug vials may not be used until IQVIA representatives (eg, IQVIA CRA) has conveyed a determination about these specific study drug 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 study drug product, whether empty or containing study drug, will be kept at the site. Study drug vials are single-use only; therefore, contents of partially used study drug vials may not be dispensed again, even to the same subject, nor relabeled or reassigned for use by other subjects. Unused study drug vials will be available for verification by the study monitor. Once dispensed, used study drug vials will be stored in a limited access area under appropriate environmental conditions.

At each investigational site closeout visit and end of clinical trial, a final study drug vial accountability review and reconciliation must be completed by the Sponsor or its representatives and any discrepancies must be investigated and their resolution documented. All study drug product vials will be destroyed at the investigational site as per institutional SOPs, after site closeout has been completed or if approved by the Sponsor or its representative as required by the site (ie, space limitations, policy) once drug accountability is conducted by the IQVIA Biotech CRA. A copy of the site destruction SOP must be maintained on file and available for the IQVIA Biotech CRA. If unable to destroy on site, please inform the IQVIA Biotech CRA.

Details of the study drug storage and handling are provided in the Pharmacy Manual.

6.4. Study Drug Dispensing

CMP-001 will be dispensed, prepared, and administered according to the 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. CMP-001 study drug is dedicated to each study and is labeled specifically for each CMP-001 study. Only authorized and qualified site staff may dispense, prepare, or administer CMP-001.

Nivolumab will be dispensed, prepared, and administered according to the Pharmacy Manual 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(s) (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 (ie, white, black or African American, Asian, American Indian/Alaskan Native, Native Hawaiian/other Pacific Islander, or other).

7.1.4. Melanoma History

Eligible subjects must have been diagnosed with a histopathologically-confirmed diagnosis of metastatic malignant or unresectable melanoma. Subjects with uveal, acral, or mucosal melanoma are not eligible.

Documentation, including radiographic and/or photographic images at baseline or at the time of response and from 2 consecutive scans separated by at least 4 weeks that demonstrate confirmed disease progression during or within 12 weeks of prior treatment that included PD-1 blockade with an FDA-approved PD-1 blocking antibody, must be reviewed by the investigator at Screening to meet eligibility (see Section 7.2.). These images should be sent/uploaded for central review for post-enrollment verification and endpoint assessment. If necessary, additional prior images may be requested for central review.

For subjects with relapse/recurrence on or after adjuvant PD-1 blocking antibody, a histological confirmation of recurrence is required. In such cases required images include imaging at initiation of adjuvant therapy demonstrating no evidence of disease and images demonstrating relapse/recurrence; images are not required for confirmation of progression. These images should be sent/uploaded for central review.

At Screening, a detailed melanoma history will be obtained, including date of initial diagnosis, American Joint Committee on Cancer (AJCC) melanoma cancer staging at diagnosis, and BRAF mutation status including treatment with a kinase inhibitor targeted for BRAF mutation (with or without a MEK inhibitor). BRAF mutation status must be assessed with an FDA-approved test. Sites should refer to the Eighth Edition AJCC Cancer Staging Manual (Amin-2017) for cancer staging.

Programmed death-ligand 1 expression status from prior biopsies, if available, will be recorded in the EDC.

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. Data on prior surgical procedures related to melanoma will also be captured in the EDC.

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 melanoma, and any reported conditions affecting major body systems during the 10 years before Screening.

7.1.7. Medication History

All medications (see Section 5.2.) administered to the subject from 30 days before first dose of study treatment (W1D1) until 100 days after discontinuation of both CMP-001 and nivolumab will be recorded in EDC. Treatment medications for AEs related to study treatment that occur more than 100 days after the last dose of study treatment will also be collected. Documentation for each medication will include the generic name of the medication, total daily dose, route of administration, dates of administration, and indication for use. Combination drugs must be listed separately by each component study treatment and dose. Prior cancer treatment will be recorded separately.

7.1.8. 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 nivolumab is administered, vital signs must be collected before the start of the nivolumab 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 for all subjects. Sites are, however, to capture oxygen saturation (and FiO2, if available) at every time point only for subjects in whom an AE of hypoxia or CRS is reported.

7.1.9. 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).

7.1.10. 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 exams

focused on areas of disease or AEs may be performed at any clinically indicated time but must be obtained before the 1st, 3rd, and 7th weekly CMP-001 injections (W1D1, W3D1, W7D1), and at each CMP-001 injection visit thereafter. Height will be obtained at Screening only and weight at all physical examination assessments. Body mass index (BMI) will be calculated by the EDC system each time weight is entered.

7.1.11. 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 interval, QRS, QT, and QT corrected heart rate intervals. QT will be corrected using Fridericia's (QTcF) formula. Electrocardiograms 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.

7.1.12. 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 3) to be obtained include:

- Hematology, chemistry, and urinalysis assessments
- Coagulation (PTT, PT, and INR) assessments
- Thyroid function tests (thyroid stimulating hormone, Free T3, and Free T4) for clinical signs and symptoms of thyroid disorder
- Autoimmune panel
- Adrenal function tests, if indicated
  - NOTE: At Screening, patients 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 B/C, 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 local and 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 as medical history if before CMP-001 dosing at W1D1, or AEs following CMP-001 dosing at W1D1 in the eCRF.

Table 3: Clinical Laboratory Assessments

Hematology	Serum Chemistry	Urinalysis	Other Laboratory Tests
RBCs WBCs Differential WBC count Total leukocyte count, including differential Hemoglobin Hematocrit Platelets	Alanine aminotransferase Albumin Alkaline phosphatase Amylase Aspartate aminotransferase Bilirubin Blood urea nitrogen or serum urea Calcium Chloride Creatinine Glucose Lactate dehydrogenase Lipase Phosphorous Potassium Sodium Total protein	Blood Glucose Nitrites pH Protein Specific gravity WBCs **Microscopic battery:** RBCs, WBCs, epithelial cells, casts (only if significant positive findings on urinalysis)	**Coagulation:** PTT PT INR **Thyroid Function Studies:** TSH, Free T3, Free T4 (at Screening) **Autoimmune laboratory panel:** Anti-dsDNA, antinuclear antibody, antineutrophil cytoplasmic antibody, rheumatoid factor, and antibodies to ribonucleoprotein (anti-RNP) **Tests to be performed as clinically indicated:** Adrenal function tests NOTE: At Screening, patients 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. 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; TSH = thyroid stimulating hormone; WBC = white blood cell.
NOTE: Refer to the 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.

7.1.13. Pregnancy Testing

Pregnancy testing will be performed on women of childbearing potential at the time points specified in the Schedule of Assessments (Table 1). A central serum pregnancy test is required during Screening. 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. Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) before dosing at W1D1 as specified in Table 1. Urine pregnancy testing will be completed for time points after Screening. 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.

7.2. Disease Assessments

Disease assessments (radiographic, photographic, and CNS imaging) will be collected according to the Schedule of Assessments (Table 1). Imaging that demonstrates confirmed disease progression must be reviewed by Investigator to define eligibility and should be provided for post-enrollment review by a BICR to verify subject eligibility and endpoint assessment (see Section 7.2.3.). Baseline imaging should be performed within 30 days of W1D1. On-study disease assessments (radiographic, photographic, 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 per RECIST v1.1 (see Appendix D).

The same disease assessment method(s) (ie, CT, MRI, photographs) used during Screening 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.

Baseline CNS imaging by contrast-enhanced CT or MRI must be provided at Screening; on-study CNS imaging is required in presence of clinical symptoms or if CNS disease was present at Baseline.

All disease assessments will be evaluated by BICR according to RECIST v1.1, and by Investigator according to RECIST v1.1 (see Appendix D), iRECIST (see Appendix E), and itRECIST (Appendix F).

All scans should be performed at least 2 weeks after the most recent CMP-001 IT injection to account for an injection-related pseudoprogression.

All radiographic and photographic images should be uploaded into the imaging portal within 1 week of completion to enable BICR (see imaging guidelines).

7.2.1. Radiographic Imaging

Contrast-enhanced CT and MRI are the preferred 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.

Any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled timepoints and/or at an outside institution) should be collected for RECIST 1.1 tumor assessment and submitted to the BICR.

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

7.2.2. Photographic Imaging

Digital photographic images of CMP-001 target and non-target skin lesions, including caliper measurements of superficial cutaneous lesions, will be obtained per the time points specified in the Schedule of Assessments (Table 1). These photos will be utilized for response assessment by the BICR. If available, historic photos collected at screening may be used by the BICR to verify subject eligibility post enrollment. Photos should be taken with a digital camera of adequate resolution according to the imaging guideline. To clearly capture the morphology of the tumor, both the skin lesion and the surrounding tissue must be included in the field of view. Each lesion should be clearly labeled with a unique identifier which must be used throughout the study. A metric ruler must also be included in the photograph field of view as a size reference.

A target lesion(s) not intended for intratumoral 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 imaging guidelines for further guidance.

7.2.3. Eligibility Disease Assessment

7.2.3.1. Confirmation of Disease Progression on Prior PD-1-blocking antibody

Investigator must review and confirm subject eligibility before initiation of study treatment. Disease assessments (radiographic and/or photographic imaging) at 3 timepoints at minimum must be reviewed by Investigator to verify eligibility. Subjects must have a baseline image or images at the time of response to prior PD-1-blocking antibody AND images at the time of progression AND confirmatory images of progression performed consecutively at least 4 weeks apart. PD according to RECIST v1.1 should be established during or within 12 weeks of the last dose of a PD-1 blocking antibody (either monotherapy or combination therapy). The confirmatory scan may serve as the Baseline for this study if completed within 30 days before the start of study treatment. A target lesion(s) not intended for intratumoral injections should be clearly labeled in the baseline imaging.

In subjects with recurrence on or within 12 weeks of completion of an adjuvant PD-1-blocking antibody a histological confirmation of recurrence is required. In subjects with histologically confirmed recurrence, confirmatory image is not required.

All images used to define subject eligibility must be submitted to BICR for post-enrollment eligibility verification.

7.2.3.2. Central Nervous System Imaging

Baseline brain imaging by contrast-enhanced CT or MRI (per site local standards) must be provided and reviewed by BICR to verify subject eligibility post enrollment.

Subsequent 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).

The volume and inflammation from an IT injection of CMP-001 may cause a tumor to transiently enlarge leading to an inaccurate assessment. All scans should be performed predose and at least 2 weeks after the most recent CMP-001 IT injection to account for injection-related pseudoprogression.

7.2.4.1. Disease Assessment Beyond Progressive Disease

Subjects with PD per RECIST v1.1 as determined by Investigator assessment who are clinically stable should remain on treatment and have a follow-up scan performed at least 4 weeks after the initial date of PD to confirm progression per RECIST v1.1. Subjects who receive study treatment beyond PD per RECIST v1.1 will have subsequent disease assessments evaluated using iRECIST by the Investigator. Disease assessments should continue according to the Schedule of Assessments (Table 1).

7.2.4.2. Confirmation of Response

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

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 Analyses

Blood samples, including serum and/or plasma, will be collected for exploratory 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 melanoma, 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 nivolumab, and subsequent exploration of factors associated with response or resistance to CMP-001 in combination with nivolumab. These samples may also be 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 PD-L1 Staining and Translational Analyses

Fresh tumor tissue biopsy samples are preferred, if safe and medically feasible, as specified in the Schedule of Assessments (Table 1). If in the Investigator's opinion it is unsafe to perform a new biopsy, archival material can be used as a substitute for analysis of PD-L1 expression if no intervening therapy was received.

The decision and rationale to forego biopsy samples at screening or during the treatment period 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 melanoma, cancer immunotherapy, or TLR9, including but not limited to RNA analyses to monitor gene expression and DNA analyses to identify mutations associated with cancer. These findings may be analyzed for association with observed clinical response, resistance, and/or AEs to the combination of CMP-001 and nivolumab.

Additional tumor biopsies may be collected during the study at the discretion of the Investigator.

7.4. Pharmacokinetic Assessments

7.4.1. Collection of Blood Samples for Measurement of CMP-001 Concentration in Serum

Venous blood samples will be collected in the first 20 subjects enrolled for measurement of CMP-001 concentrations.

If the CMP-001 dose is divided across multiple tumors, sample collection times will be relative to the time of the first tumor injection.

Blood will be obtained by either direct venipuncture or from an indwelling cannula inserted in a forearm vein, whenever possible. Samples collected on the same day of dose administration should be collected in the contralateral (opposite) side of the body from the one where CMP-001 is administered (if administered into a tumor on the extremities). Refer to Table 1 for acceptable collection windows.

Additional detailed instructions for the blood collection, processing, storage, and shipment to the bioanalytical laboratory will be detailed in the Laboratory Manual.

Blood will be collected before CMP-001 injection at Weeks 1, 6, and 7. Blood will be collected following CMP-001 dosing at Weeks 1 and 6. Samples will continue to be collected according to the Schedule of Assessments (Table 1).

7.4.2. Measurement of CMP-001 Concentration in Blood Samples

Samples for the determination of CMP-001 concentrations in blood will be analyzed by a bioanalytical laboratory under the responsibility of the Sponsor using appropriate validated bioanalytical methods.

Samples that meet the criteria of the bioanalytical laboratory's SOPs (ie, condition upon receipt, stability, etc.) will be analyzed in accordance with the bioanalytical laboratory's SOP(s), the validated method, and the bioanalytical sample analysis plan. Full details of the bioanalytical methods and batch performance will be described in a separate Bioanalytical Report.

Remaining blood samples may be subjected to further analysis by the Sponsor or its representatives for the development of additional bioanalytical assays and/or for further investigation of CMP-001 stability/degradation. Samples collected for analyses of CMP-001 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

7.4.3. 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 CRS are experienced.

7.5. Immunogenicity Sampling

Blood samples will be collected for immunogenicity (anti-Qb antibodies) at the time points specified in the Schedule of Assessments (Table 1).

Samples for nivolumab immunogenicity may be evaluated for development of anti-drug antibody (ADA). Samples may also be analyzed for neutralizing antibodies. If applicable and within the same matrix, PK samples may be used for ADA analysis in the event of insufficient volume, to complete immunogenicity assessment, or to follow-up on suspected immunogenicity-related AEs.

The procedures for sample collection, processing, storage, and shipment are provided in the Laboratory Manual.

7.6. 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). All AEs/SAEs will be captured from the time of ICF and recorded on the eCRF as AEs. All other medical occurrences (non-adverse events) that begin before start of study treatment should be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section. All AEs reported on or after the date that study treatment was first administered (W1D1), will be recorded on the eCRF and will be considered treatment-emergent adverse events (TEAEs). All TEAEs, defined as an AE that started or worsened in severity on or after the date that study treatment was first administered (W1D1), will be graded according to CTCAE v5.0 (Appendix C) and coded using Medical Dictionary for Regulatory Activities (MedDRA). Worsening TEAEs (ie, 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.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on-site/local labs until all study treatment-related toxicities resolve, return to Baseline, or are deemed irreversible.

If a participant shows cardiac or pulmonary-related signs (hypoxia, abnormal heart rate, or changes from Baseline) or symptoms (eg, dyspnea, cough, chest pain, fatigue, palpitations), the participant should be immediately evaluated to rule out cardiac or pulmonary toxicity.

Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

7.6.1. Adverse Events

AEs should be monitored from the time that the informed consent is signed through 100 days after the last dose of study treatment (both CMP-001 and nivolumab) or until an alternative cancer treatment is initiated, whichever occurs first, for all subjects. All AEs from the time that the informed consent is signed will be captured on the eCRF. Subjects who discontinue CMP-001 but remain on treatment with nivolumab will continue to have AEs collected according to this schedule until 100 days after the last dose of nivolumab or until an alternative cancer treatment is initiated, whichever occurs first.

Treatment-related SAEs starting more than 100 days after the last dose of study treatment will be recorded on the AE eCRF.

Immune-mediated AEs are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. Immune-mediated AEs can include events with an alternate etiology that were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's case report form.

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

7.7. 100-Day Follow-up Contact

The 100-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.

7.8. 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).

Posttreatment follow-up disease assessments will continue until disease progression, initiation of another cancer treatment, death, loss to follow-up, withdrawal of consent, or End of Clinical Trial.

7.9. 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.

In this study, OS is a key endpoint of the study. Post-study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required until death or the conclusion of the study.

The Sponsor may request that survival data be collected on all treated participants outside of the protocol defined window (Schedule of Assessments, Table 1). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contacts or is lost to follow-up.

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 treatment (active or placebo drug, biologic, or device) in clinical investigation subjects, which does not necessarily have a causal relationship with the study treatment. An AE can therefore be any unfavorable and unintended symptom, sign, disease, condition, or test abnormality whether or not considered related to study treatment (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 (eg, laboratory tests) that result in an alteration in medical care (diagnostic or therapeutic) and/or are considered clinically significant by the Investigator

Immune-mediated adverse events are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. Immune-mediated AEs can include events with an alternate etiology that were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's case report form.

Every adverse event must be assessed by the Investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's case report form.

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 Table 4.

Table 4: Criteria for Determination of Serious Adverse Events

Death	An 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 (ie, 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 treatment, 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 treatment.
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.

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; SAE = serious adverse event; W1D1 = Week 1 Day 1.

a. Planned hospital admissions or surgical procedures for elective procedures or an illness or disease that existed before the time of consent will not be captured as SAEs. If there was a change in medical condition it may be an SAE.

Appendix C: CTCAE v5.0

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 treatment.

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

8.1.3. Definition of a Treatment-Emergent Adverse Event

A TEAE is defined as an AE that started or worsened in severity on or after the date that study treatment was first administered (W1D1) until 100 days after the last dose of study treatment or until an alternative cancer treatment is initiated, whichever occurs first

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 v5.0), causality/relationship to CMP-001 and to nivolumab 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 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 for nivolumab.

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 v5.0 (Appendix C).

Note that severity is not the same as seriousness (defined in Table 4). Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Worsening of an ongoing TEAE (ie, 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 5: 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 AE

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events.
Appendix C: CTCAE version 5.0

8.2.2. Relationship to Study Treatment

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 6 (see Appendix C). Attribution of AEs will be determined for each of the individual components (CMP-001 and nivolumab) 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 6: Classification for Adverse Event Causality

Classification	Definition
Unrelated	There is no suspicion of a causal relationship between exposure to the study treatment regimen and the AE; another cause of the AE has been identified, no temporal association with study treatment has been identified, or the study treatment cannot be implicated
Possibly related	There is some evidence supporting the possibility of a causal relationship between study treatment regimen exposure and the AE; an alternative explanation (ie, concomitant drug or concomitant disease) is inconclusive, the temporal association with study treatment is reasonable, and the causal relationship cannot be excluded
Probably related	An AE that has a timely relationship to the administration 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 treatment regimen and the AE; the AE cannot be reasonably explained by an alternate explanation (ie, concomitant drug or concomitant disease) and the temporal association with study treatment is suggestive of a causal relationship

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events.
NOTE: CMP-001 and nivolumab 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

Every AE must be assessed by the Investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's case report form.

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 Table 7.

Table 7: 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	AE has resolved, but the subject has been left with symptoms or pathology
Unknown	Not known, not observed, not recorded, or refused

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events.
Appendix C: CTCAE version 5.0

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

The Investigator will provide the action taken regarding study treatment separately for CMP-001 and nivolumab in response to the AE. Refer to Section 5.1.3. and Section 5.1.5. for

CMP-001 and nivolumab allowed dose modifications. Classifications for each of the potential actions taken are provided in Table 8.

Table 8: Classifications for Actions Taken Related to Study Treatment Administration Regarding an Adverse Event

Classification	Definition
No change	No change in administration of study treatment
Study treatment delayed	Temporary delay in administration of the study treatment
Study treatment withheld	1 or more planned doses of study treatment completely withheld (skipped)
Study treatment permanently withdrawn	Administration of the study treatment 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 study (Title 21 Code of Federal Regulations [CFR] Part 312.64[b] and International Council for Harmonisation [ICH] E6 entitled "Guideline to Good Clinical Practice"). At each study visit, subjects will be evaluated for new AEs and the status of existing AEs. All AEs/SAEs will be captured from the time of ICF and recorded on the eCRF as AEs. All other medical occurrences (non-adverse events) that begin before start of study treatment should be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section. All AEs reported on or after the date that study treatment was first administered (W1D1), will be recorded on the eCRF and will be considered TEAEs. Treatment-emergent adverse events observed until 100 days after the last dose of study treatment (both CMP-001 and nivolumab) or until an alternative cancer treatment is initiated, whichever occurs first, 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 nivolumab will be recorded for all AEs. Adverse events starting more than 100 days after the last dose of study treatment should not be recorded on the AE eCRF unless they are serious and 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: Safety-Inbox.Biotech@IQVIA.com or by fax to: +1 866-761-1274 as backup 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 the individual components (CMP-001 and nivolumab) of the study treatment; and action taken regarding the study treatment will be recorded. Vital signs, laboratory results, and other safety assessments noted in Section 7.1.8. 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 treatments. 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.

Serious adverse events will be collected from the time of ICF until 100 days after the last dose of study treatment or until an alternative cancer treatment is initiated, whichever occurs first. Any SAE considered to have at least possible relationship to the study treatment and discovered by the Investigator at any time period after EOT should be reported throughout the study period.

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 treatment (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 ID number, period of study treatment intake, event term, nature of the event, detailed description of the event, seriousness criteria, causality of the event to CMP-001 and to nivolumab 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 treatment information including doses, dates of dosing, and action taken with individual study treatments

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 treatments. 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 representative 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 dose of study treatment 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 treatment. The progress of the pregnancy must be followed until the outcome of the pregnancy is known (ie, 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 SAE. Pregnancy should not be entered into the eCRF as an AE unless the Investigator suspects an interaction between the study treatment 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 (unexpected SAEs that are determined to be associated with the use of study treatment) 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 United States, 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 treatment. 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 adverse events and AEs resulting in discontinuation will be followed until 1 of the following occurs:

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

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 (ie, 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:

Safety-Inbox.Biotech@IQVIA.com.

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 treatment, 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, 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 v9.4 or higher.

9.1. Sample Size Calculation

This study will enroll approximately 100 subjects. A subject is enrolled in the study when they have received the first dose of study treatment. 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.

A sample size of 69 subjects achieves at least 90% power to detect a difference of 13% using a 2-sided exact test with a significance level of 0.05, assuming that the null hypothesis for ORR is 7% (Hodi-2016; Ribas-2018), and the study ORR is 20%. The sample size was increased to 100 subjects to adjust for an early discontinuation rate of 15% and to allow for a robust assessment of safety. A sample size of 100 subjects with an ORR of 20% produces a 95% Clopper-Pearson CI for the ORR of 12.7% to 29.2% (PASS 2020).

Blood samples for PK analysis will be collected from approximately 20 subjects.

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 treatment.

9.2.2. Safety Analysis Set

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

9.2.3. Per Protocol Analysis Set

The Per Protocol Analysis Set is defined as all subjects who receive at least 1 dose of study treatment and are without major protocol deviations.

9.2.4. Pharmacodynamic Analysis Set

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

9.2.5. Pharmacokinetic Analysis Set

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

9.2.6. Immunogenicity Analysis Set

The Immunogenicity Analysis Set is defined as all subjects who receive CMP-001 and have evaluable samples for immunogenicity 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 treatment), discontinue study treatment, and 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. ECOG Performance Status

Eastern Cooperative Oncology Group 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. Melanoma History

Melanoma history (time since initial diagnosis, tumor stage, nodal status, and metastatic disease status at time of initial diagnosis) will be summarized using descriptive statistics for the ITT Analysis Set and listed by subject. Melanoma history will be captured on a separate eCRF in the EDC system.

9.3.5. Prior Cancer Treatments

All prior melanoma treatments 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 treatment and discontinued before the first dose of study treatment.

Concomitant medications will be assessed continually from 30 days before the first dose of study treatment (W1D1) through 100 days after the last dose of study treatment (both CMP-001 and nivolumab) or until an alternative cancer treatment is initiated, whichever occurs first. Treatment medications for study-related AEs that occur more than 100 days after the last dose of study treatment will be collected.

Medications will be coded using the World Health Organization drug dictionary and summarized according to the Anatomical Therapeutic Chemical 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 Anatomical Therapeutic Chemical class and preferred term in the summary tables.

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

9.4. Study Treatment Exposure and Compliance

The number of CMP-001 and nivolumab 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.

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

9.5. Efficacy Analyses

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

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 BICR.

The confirmed ORR is defined as the proportion of 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 = (confirmed CR + confirmed PR)/number of subjects] for the ITT Analysis Set. Ninety-five percent Clopper-Pearson CIs for the ORR 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 analyses will be the comparison of the study BICR RECIST v1.1 confirmed ORR to a 7% ORR assumed under the null hypothesis (Hodi-2016) using a 2-sided exact test for the ITT Analysis Set.

The objective response rate per RECIST v1.1, iRECIST, and itRECIST by Investigator assessments will also be summarized.

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 stable disease (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 SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

9.5.3. Treatment Effect in Non-injected Target Lesions

The treatment effect in non-injected target lesions will be assessed separately from the overall effect. The confirmed ORR in non-injected target lesions based the RECIST v1.1 BICR measurements will be summarized.

9.5.4. Duration of Response

Duration of response will be based on RECIST v1.1 as determined by BICR and calculated for responders.

The DOR will be measured from the time at which criteria are first met for CR or PR (whichever is first recorded) until the first date that recurrence or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study). 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.

Duration of response and iDOR will also be determined by Investigator assessment per RECIST and iRECIST.

9.5.5. Progression-Free Survival

Progression-free survival is defined as the time from first dose of study treatment to the date of documented PD based on RECIST v1.1 by BICR or death from any cause, whichever occurs first. Subjects who are alive and progression-free at the time of analyses will be censored in the analyses. Additional censoring rules may be defined in the SAP. Median PFS will be calculated using the Kaplan-Meier method.

Analysis of PFS and iPFS based on RECIST v1.1 and iRECIST determined by Investigator assessment will also be performed.

9.5.6. Overall Survival

Overall survival will be calculated as the time from first dose of study treatment to the date of death due to any cause. Subjects who are alive at the time of analyses will be censored at the time of last study contact. Median OS will be calculated using the Kaplan-Meier method.

9.5.7. Post-Progression Disease Response

Post-progression disease assessments of tumor response based on iRECIST by Investigator assessment will be summarized.

9.5.8. Exploratory Efficacy Analyses

Exploratory efficacy analyses may also be performed to evaluate the effect of CMP-001 in combination with nivolumab on injected and noninjected target lesions. These analyses will be based on itRECIST (Goldmacher-2020) (Appendix F) by Investigator assessment and may include ORR in noninjected target lesions, the maximal size reduction for each injected target lesion, the time until IT therapy is determined to stop providing benefit to the injected target lesions, and the time until the first instance of PD in the injected target lesions.

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

Treatment-emergent adverse events 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 (ie, system organ class or preferred term) will be counted only once in that level using the most severe event or most related (for the relationship to study treatment tables).

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, related SAEs, and TEAEs leading to treatment discontinuation.

A by-subject AE data listing, including verbatim term, system organ class, preferred term, treatment, grade, outcome, and relationship to treatment for CMP-001 and nivolumab 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. Within normal limits 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 local and 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 PK Analysis Set. Pharmacokinetic 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, time of maximum observed serum concentration, area under the serum concentration-time curve from time zero to the last quantifiable time point, area under the serum concentration-time curve from time zero extrapolated to infinity, and terminal elimination half-life.

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

9.8. Pharmacodynamic Analyses

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

9.9. Immunogenicity Analyses

Immunogenicity data based on anti-Qb antibodies will be summarized descriptively for the Immunogenicity Analysis Set.

9.10. Exploratory Tumor Biopsy Analyses

Tumor biopsy obtained at Baseline and specified time points during the study may be analyzed for protein, RNA, DNA, or other biomarkers related to TLR9, immune checkpoints, and potential markers of resistance or response to immunotherapy for the Pharmacodynamic Analysis Set.

9.11. Appropriateness of Measures

The safety assessments in this protocol (ie, physical examination, vital signs, hematology, serum chemistry, urinalysis, coagulation, thyroid function, AEs, 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.

9.11.1. Blinded Independent Central Review Committee

Blinded Independent Central Review will be used for the primary efficacy assessments of tumor response. A detailed charter for the BICR will be created before the first BICR assessment.

Blinded Independent Central Review responsibilities include verification of disease progression.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

10.1. Study Monitoring

Before an investigational site can enter a subject 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 to the Investigator(s)
- Confirm that the facilities remain acceptable
- Confirm that the study team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and the study treatment is being properly maintained and accountability records are current
- Perform source data verification with access to all original clinical records for each subject

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

10.2. Case Report Forms

Electronic Case Report Forms 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 site 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 or its representatives 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 ICF, must be approved or given a favorable opinion in writing by an IRB or Independent Ethics Committee (IEC) as appropriate. The Investigator must submit written approval to the Sponsor or its representatives before he or she can enroll any 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. The 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 the event 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 1 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 a template ICF to the Investigator. The final ICF must be approved by the Sponsor or its representatives before being reviewed and approved by the IRB. The final IRB-approved ICF 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 be 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, including 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's 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, eg, 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-1982

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

Study Phase	Estimated Blood Volume
Screening/Baseline	35 mL
Weekly Dosing (7 doses every week)	260 mL
Q3W Visits (~15 visits over 1 year)	375 mL
EOT	45 mL
PTFU	10 mL
Total Blood Volume Estimate for 1 year of study participation	725 mL (approximately 3 cups)

Abbreviations: EOT = End of Treatment; Q3W = every 3 weeks.

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 v5.0 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 5 options for Grade selection.

Activities of Daily Living

*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 (ie, ‘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 (ie, 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 (ie, 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, eg, 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, eg, 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, eg, 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, ie, 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, eg, 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, eg, 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). 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 five measurable lesions are designated as T-I and are used to evaluate the injected lesion response. One to five 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).

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). 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 (eg, 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 (eg, 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). 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 9). 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 9: 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). The injected response is based on SOD change from the previous assessment (Table 9). 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 patients 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).

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). 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 patients 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 (eg, 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 patients). 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 (eg, 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

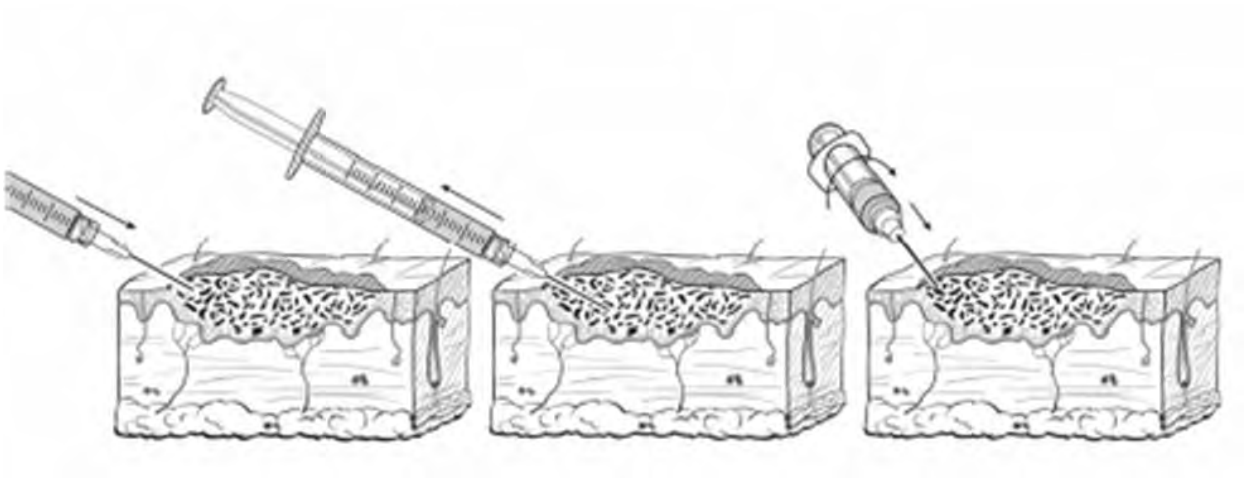
Intratumoral Injection

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 mm 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 (eg, major airways, major blood vessels).

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

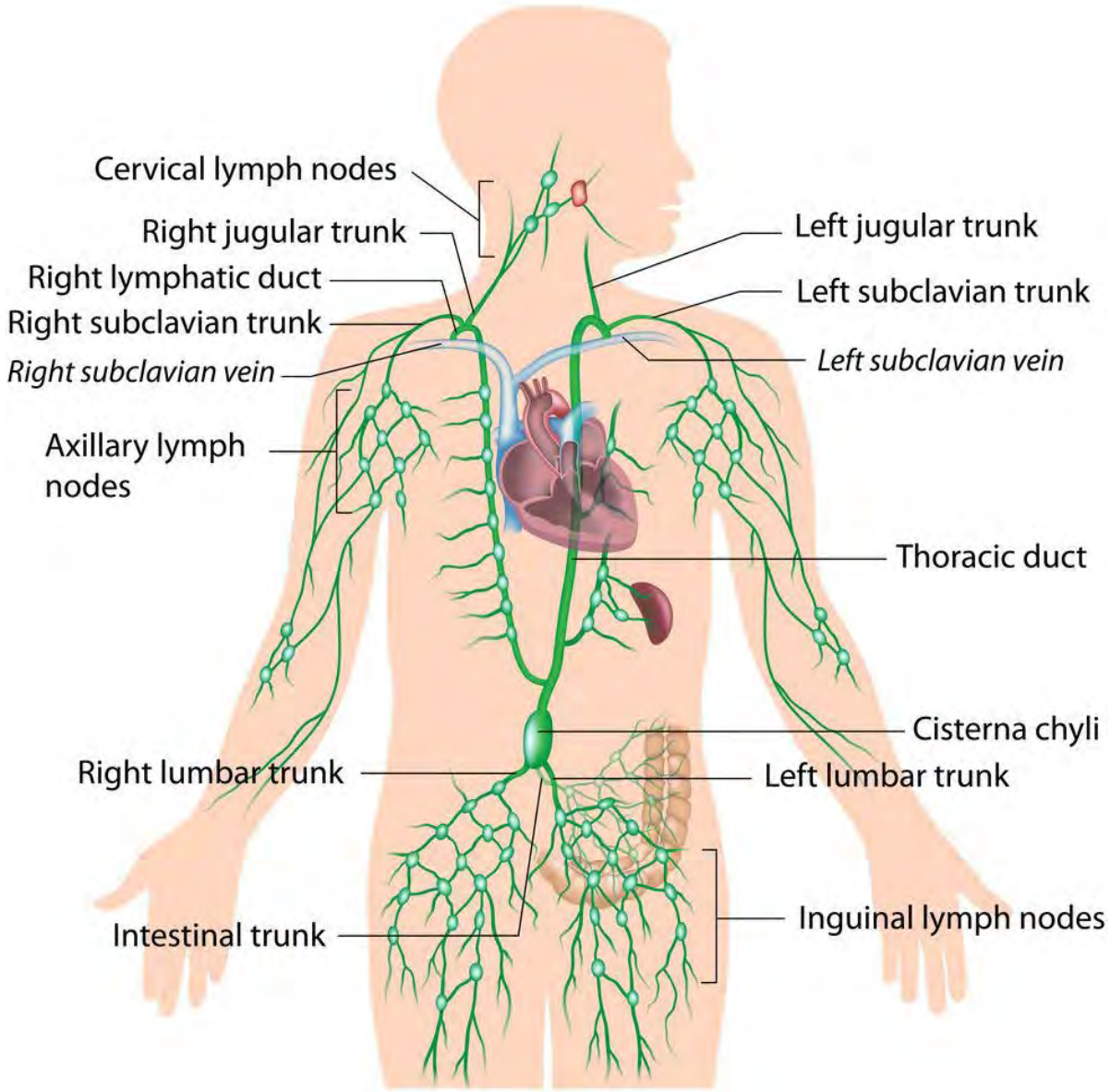
Subcutaneous administration of CMP-001 should only occur when all accessible lesions have regressed. CMP-001 SC can be administered within the area of lymphatic drainage corresponding to the site of metastatic disease and follow local standards for SC injection.

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



APPENDIX H. NIVOLUMAB SAFETY ALGORITHM

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

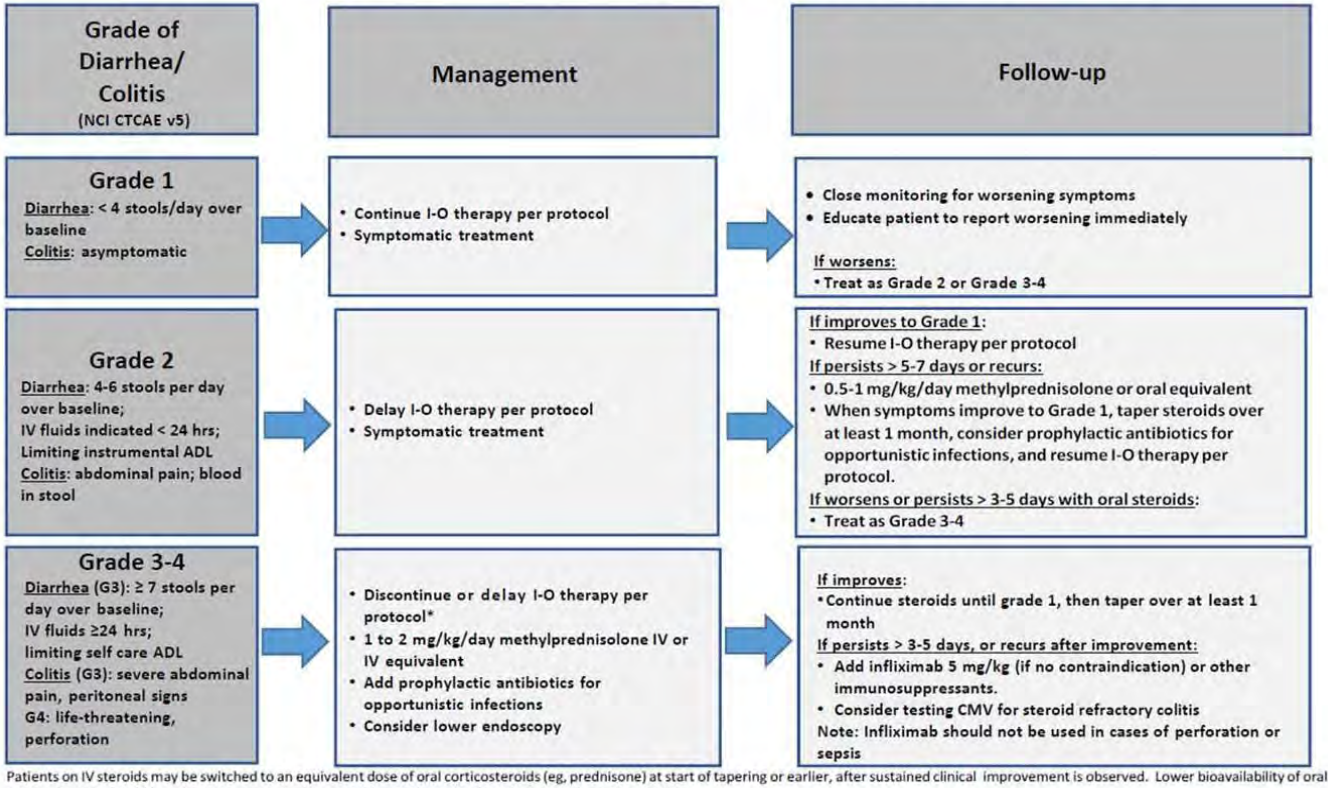
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially before an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy.
Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

* Discontinue for Grade 4 diarrhea or colitis. For Grade 3 diarrhea or colitis, 1) Nivolumab monotherapy: Nivolumab can be delayed. 2) Nivolumab+ Ipilimumab combination: Ipilimumab should be discontinued while nivolumab can be delayed. Nivolumab monotherapy can be resumed when symptoms improve to Grade 1. Please refer to protocol for dose delay and discontinue criteria for other combinations.

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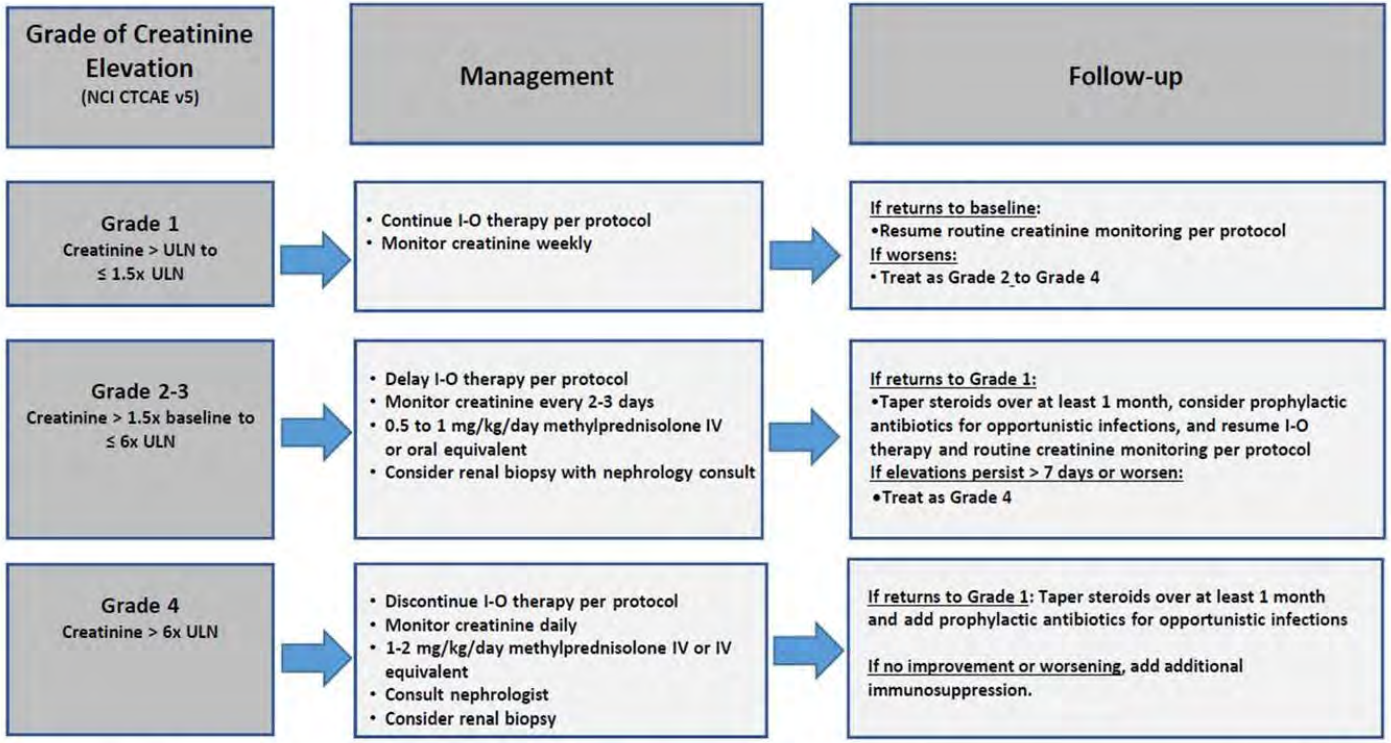
Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

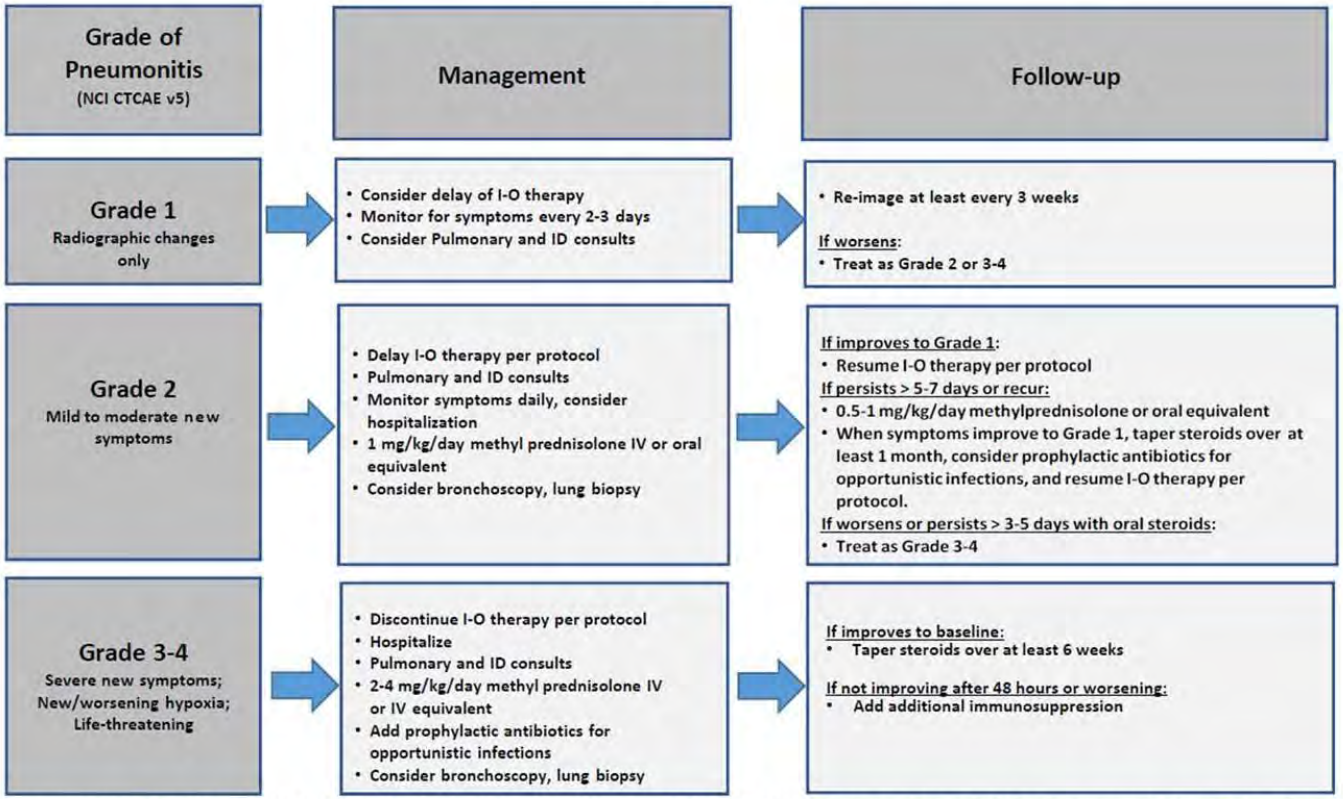


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

28-Sep-2020

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Evaluate with imaging and pulmonary consultation.

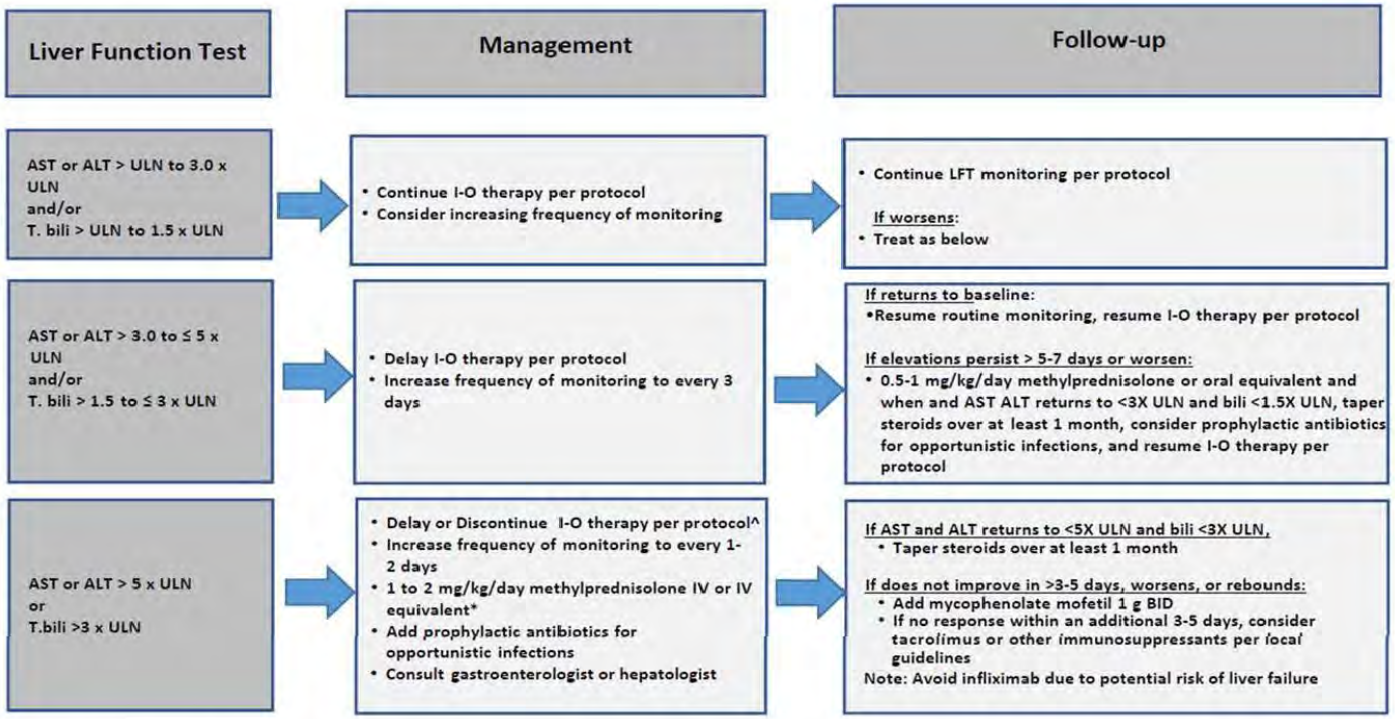


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

28-Sep-2020

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider imaging for obstruction.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
^ Please refer to protocol dose delay and discontinue criteria for specific details.
*The recommended starting dose for AST or ALT > 20 x ULN or bilirubin >10 x ULN is 2 mg/kg/day methylprednisolone IV.

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Endocrinopathy Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider visual field testing, endocrinology consultation, and imaging.

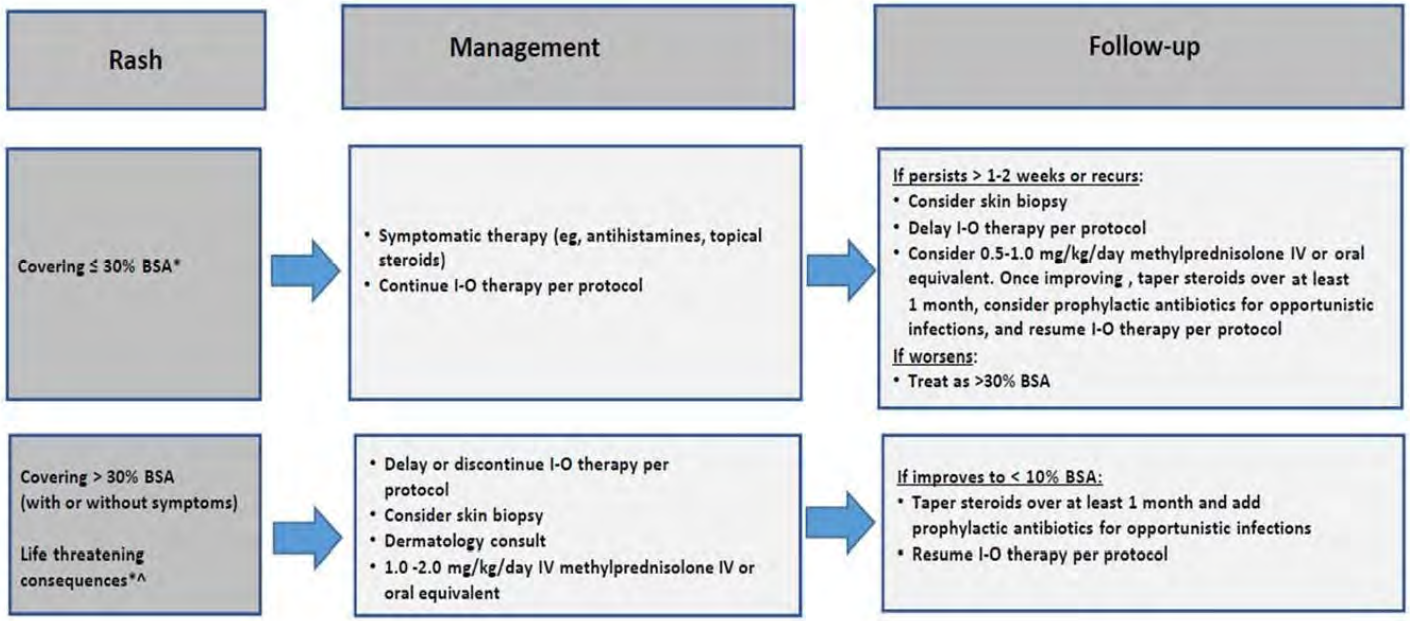
Endocrinopathy	Management	Follow-up
Asymptomatic TSH abnormality or Hyperglycemia requiring no medical intervention	• Continue I-O therapy per protocol • If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: ○ include fT4 at subsequent cycles as clinically indicated; ○ consider endocrinology consult	• Monitor TSH as per protocol • Monitor blood sugar • If symptomatic or blood sugar requiring initiation of treatment or change in management, manage as below
Symptomatic endocrinopathy or hyperglycemia requiring initiation of treatment or change in daily management or work up	• Evaluate endocrine function; consider endocrinology consult • Consider pituitary scan Symptomatic with abnormal lab/pituitary scan: • Delay I-O therapy per protocol • 1-2 mg/kg/day methylprednisolone IV or PO equivalent for hypophysitis • Initiate appropriate hormone/medical therapy No abnormal lab/pituitary MRI scan but symptoms persist: • Continue IO therapy. Repeat labs in 1-3 weeks /MRI in 1 month Hyperglycemia: Screen for Diabetic Ketoacidosis (DKA). If negative, continue IO and treat diabetes. If DKA hold IO, admit, manage DKA. Steroids not recommended for DKA/hyperglycemia	If improves (with or without hormone replacement): • Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections • Resume I-O therapy per protocol • Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	• Delay or discontinue I-O therapy per protocol • Rule out sepsis • Stress dose of IV steroids with mineralocorticoid activity • IV fluids • Consult endocrinologist	• Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component • If adrenal crisis resolves and patient is adequately controlled with physiologic hormone replacement, patient can resume IO therapy per protocol.

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

28-Sep-2020

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

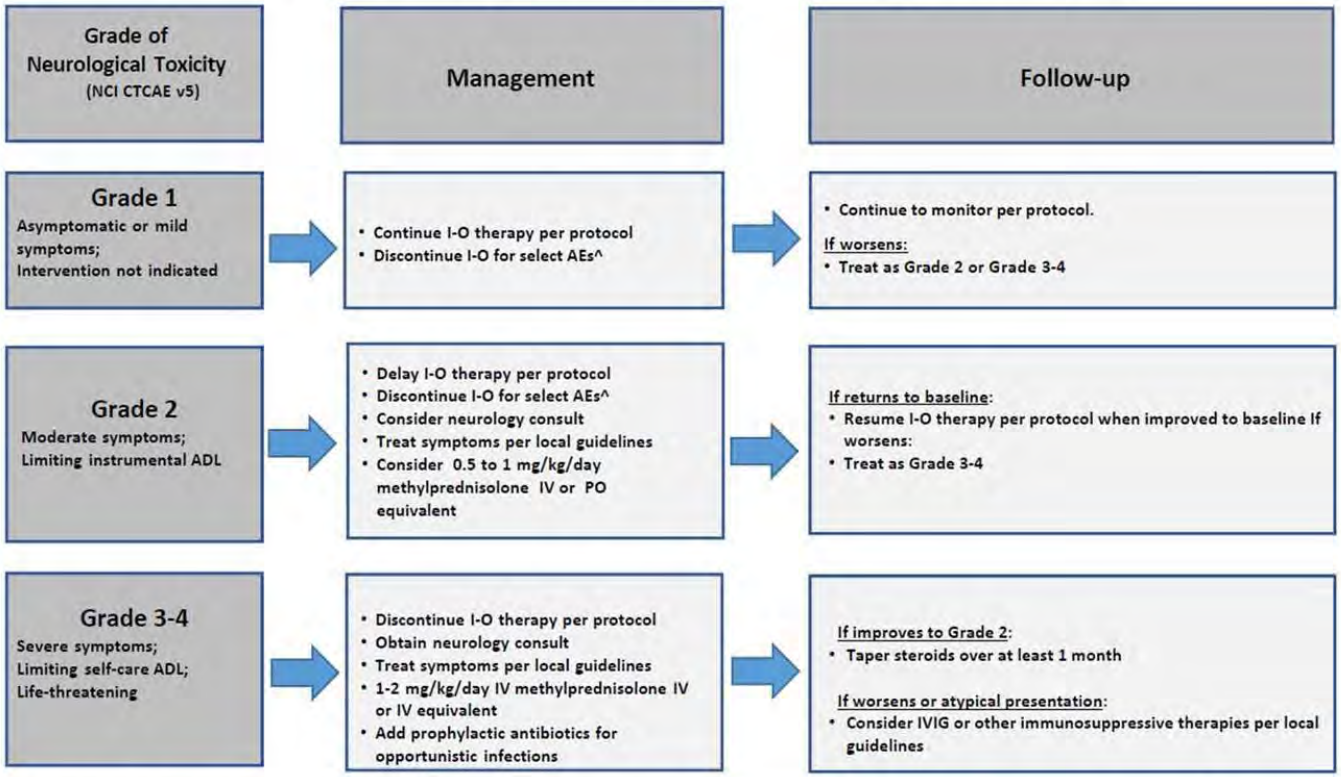
*Refer to NCI CTCAE v5 for term-specific grading criteria.

^If Steven-Johnson Syndrome (SJS),toxic epidermal necrosis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS, TEN, or DRESS is diagnosed, permanently discontinue I-O therapy.

28-Sep-2020

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



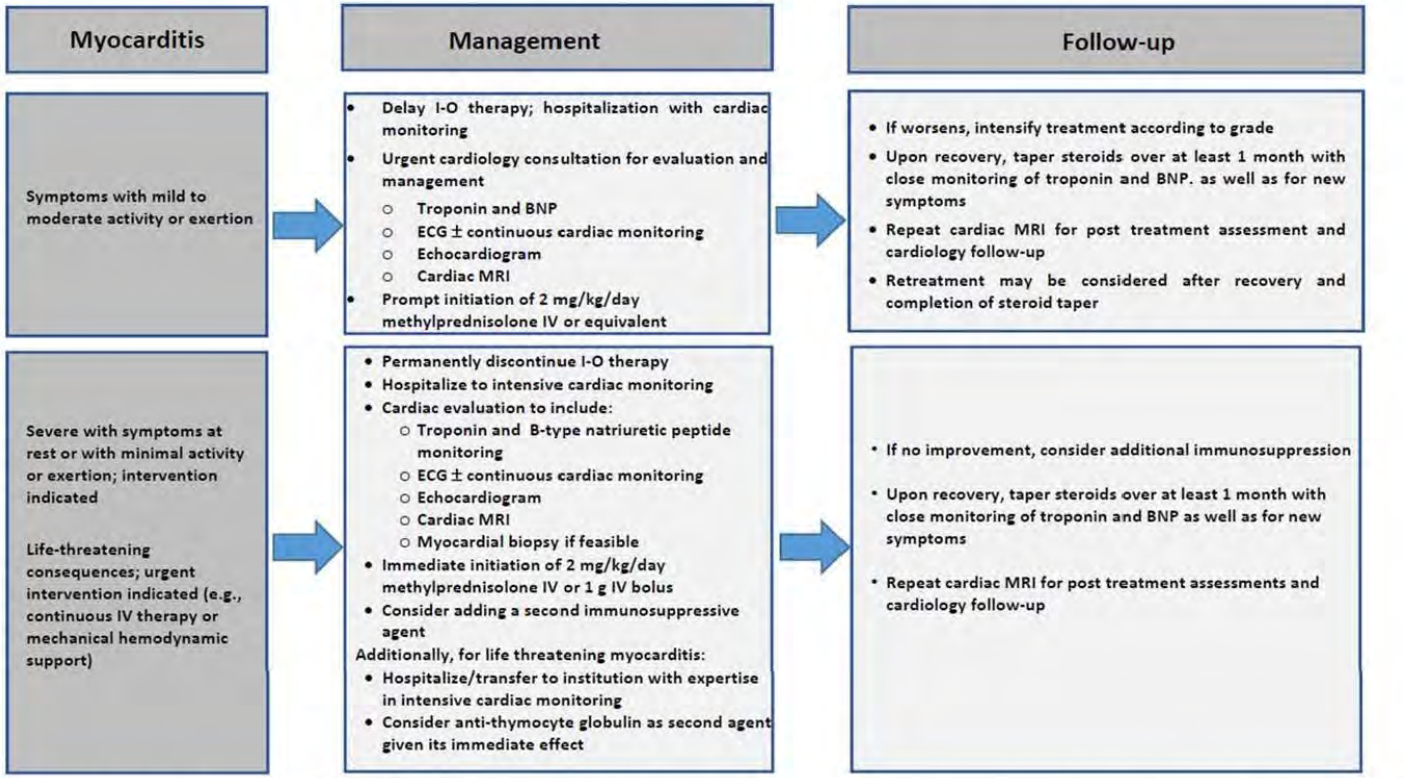
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

^Discontinue for any grade myasthenia gravis, Guillain-Barre syndrome, treatment-related myelitis, or encephalitis.

28-Sep-2020

Myocarditis Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

28-Sep-2020

APPENDIX I. COUNTRY-SPECIFIC REQUIREMENTS FOR HIV TESTING / EXCLUSION

Certain countries may require additional parameters for exclusion of HIV-positive participants which are locally mandated.

As needed, the following table can be used to identify the changes needed to adapt the protocol to suit these local requirements.

Original language	Country-specific language
Section 4.1 Exclusion Criterion #16	TBD
Section 7.1.12 Clinical Laboratory Assessments, Table 3	TBD
Table 1, Schedule of Assessments	TBD

APPENDIX J. WOMEN OF CHILDBEARING POTENTIAL DEFINITION AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment.*

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable

Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Unacceptable Methods of Contraception*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action

• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

Local laws and regulations may require use of alternative and/or additional contraception methods.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy is provided in Section 7.1.13. and Section 8.3.2.

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