SPONSOR: University of Iowa

TITLE: Phase I/II study of Pembrolizumab and in-situ injection of CMP-001 in Patients with Relapsed and Refractory Lymphomas

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ABBREVIATION

Abbreviation or Acronym	**Definition**
AE	adverse event
ALT	alanine aminotransferase
ANCA	Anti-Neutrophil Cytoplasmic Antibodies
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BOR	best overall response
Bpm	beats per minute (heart rate)
CFR	Code of Federal Regulations
CNS	central nervous system
CpG	cytosine linked to a guanine by a phosphate bond
CR	complete response
CRA	Clinical Research Associate
CRO	Contract Research Organization
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	cytotoxic T lymphocyte
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CVA	cerebrovascular accident
D	day
DLN	draining lymph node
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	identification
IFN	interferon
INR	international normalized ratio
IRB	Institutional Review Board
irRC	Immune-Related Response Criteria
IV	intravenous
MI	myocardial infarction
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or Acronym	Definition
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
N or n	number
OBD	optimal biologic dose
ODN	oligodeoxynucleotide
ORR	objective response rate
PD	progressive disease
PD-1	programmed cell death protein 1
pDC	plasmacytoid dendritic cells
PFS	progression-free survival
PR	partial response
PTT	partial thromboplastin time
QTc	QT corrected for heart rate
QTcF	QT corrected according to Fridericia
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	Stable disease
SOC	System Organ Class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
Th1	T helper cell type 1
TME	Tumor microenvironment
TLR9	Toll-like receptor 9
Treg	Regulatory T cell
TSH	thyroid stimulating hormone
TTR	time to response
ULN	upper limit of normal
U.S.	United States
WBC	white blood cell
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

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1.0 TRIAL SUMMARY

Abbreviated Title	**Pembrolizumab and in-situ injection of CMP-001 for Relapsed and Refractory Lymphomas**
Trial Phase	Phase I/II
Clinical Indication	Relapsed and Refractory Lymphomas
Trial Type	Single arm
Type of control	No control arm
Route of administration	Pembrolizumab intravenous injection and CMP-001 in-situ injection
Trial Blinding	No blinding
Treatment Groups	Adaptive dose-finding based on efficacy and toxicity
Number of trial participants	Maximum of 21 evaluable patients
Estimated enrollment period	3-4 years
Duration of Participation	Patient responding to treatment will be followed for 2 years. Patient progressing on treatment will come off study.
Estimated average length of treatment per patient	6 months

2.0 TRIAL DESIGN

2.1 Investigational Plan

2.1.1 Overall Study Design

This is a single center, open-label, combined Phase I/II clinical study of intratumoral administration of CMP-001 and intravenous administration of pembrolizumab in selected subjects with lymphoma. The key study objective is to find a CMP-001 dose (vidutolimod) that in combination with pembrolizumab has optimal clinical efficacy and acceptable toxicity. Dose-finding will be performed with an adaptive clinical trial design. Secondary study objectives include characterization of safety, pharmacodynamics, and assessment of anti-lymphoma activity.

Each treatment cycle is 3 weeks in duration. The first CMP-001 injection stimulates antibody formation to the VLP of CMP-001 and will be given subcutaneously. Subsequently, CMP-001 will be administered by intratumoral injection every week for seven doses. The seventh dose, which is to be administered on Week 7 Day 1 (W7D1), represents the start of dosing at 3-week intervals (ie, with subsequent CMP-001 doses to be administered on Week 10 Day 1 [W10D1] and Week 13 Day 1 [W13D1]). Subjects enrolled into this study will continue study treatment so long as they do not experience unacceptable toxicities and in the Investigator's

opinion continued treatment is in the subject's best interest. Patient will be evaluated for treatment efficacy and toxicity up to 30 days after end of treatment and followed for long term survival for 2 years.

2.1.2 Dose Finding Adaptive Design

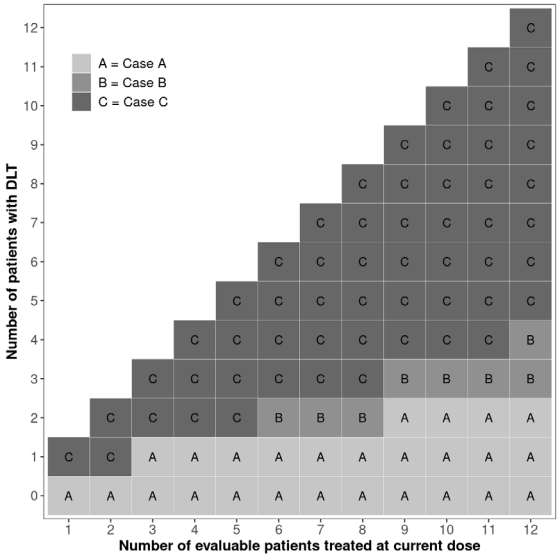
The Bayesian optimal interval design (BOIN12) of Lin et al. (Lin, Zhou, Yan, Li, & Yuan, 2020). will be used to conduct dose finding for CMP-001 across the levels summarized in **Table 1b**. Pembrolizumab dose will be fixed at 200 mg IV every 3 weeks. In the design, patients will be assigned adaptively to CMP-001 dosing cohorts to find a dose with biologically optimal efficacy and toxicity.

Table 1a: Dose Levels in the Adaptive Design

Dose Level	Pembrolizumab Dose	CMP-001 Dose (mg)
1*	Per Product Label	7.5
2	Per Product Label	10

* Starting dose

Table 1b. Decision table to choose Case A, B, or C to determine the dose assignment for new patients



A maximum of 21 patients will be treated sequentially in up to 7 cohorts of three patients each. Treatment will start in the first cohort at a CMP-001 dose of 7.5 mg. After a cohort is evaluable for efficacy and dose-limiting toxicity (DLT), the next cohort will be treated at the admissible dose with highest mean utility. Admissible dose levels (j) are determined according to the following posterior probability criteria for their true rates of DLT ($\pi_{T,j}$) and efficacy ($\pi_{E,j}$):

$$\Pr(\pi_{T,j} > 0.3 | data) < 0.925$$

$$\Pr(\pi_{E,j} < 0.5 | data) < 0.90.$$

Desirable tradeoff between treatment benefit and risk is quantified with a utility function defined by the investigators to be $\Pr(\pi_{E,j}) - 0.3\Pr(\pi_{T,j})$. If a dose is found to not meet the admissibility criteria during the trial, it will be eliminated from further enrollment. If the number of patients at the current dose reaches 12, the trial will be stopped. Specifically, dose selection in the BOIN12 design proceeds according to the following 3 steps.

1. Treat the first cohort at dose level $j = 1$.
2. Suppose that the current dose level is j, use decision Table 1a to choose one of the following three cases to determine the dose for treating the next cohort of patients.

   Case A: Determine the desirability of dose levels $j - 1$, j, and $j + 1$ using the rank-based desirability scores (RDS) given in Table A of APPENDIX F, and choose the one that has the highest desirability to treat the next cohort. If the RDS of all three doses are "E," stop the trial and no dose should be selected. In the case that dose level $j - 1$ or $j + 1$ does not exist, then apply the above rule to dose levels j and $j + 1$ (or j and $j - 1$).

   Case B: Determine the desirability of dose levels j and $j - 1$ using the RDS given in Table A of APPENDIX F, and choose the one that has the higher desirability to treat the next cohort. If the RDS of the two doses are "E," stop the trial and no dose should be selected. If the current dose level j is the lowest dose, treat the next cohort of patients at the lowest dose unless the RDS of the lowest dose is "E," at which point terminate the trial.

   Case C: Determine the desirability of dose levels j and $j - 1$ using the RDS given in Table A of APPENDIX F.

   - If the current dose level j is the lowest dose, treat the new patients at the lowest dose unless the RDS of the lowest dose is "E," at which point terminate the trial.
   - If the current dose level j is not the lowest dose and the RDS of dose level $j - 1$ is not "E," de-escalate the dose to level $j - 1$ to treat the next cohort of patients.
   - If the current dose level j is not the lowest dose and the RDS of dose level $j - 1$ is "E," stay at the current dose level j to treat the next cohort of patients unless the RDS of dose level j is "E," at which point terminate the trial.

3. Repeat step 2 until the maximum sample size of 21 is reached or if the number of patients treated on any dose reaches 12. Then, use the isotonic estimation method described in Lin et al. (Lin et al., 2020) to select the (biologically optimal) dose that is admissible and that has the highest estimated utility.

We have treated 6 patients on the study so far. The first 3 patients were treated at the dose level of 5 mg and the next 2 patients at dose level 7.5 mg. The three patients treated at 7.5 mg CMP001 dose will be included to the maximum accrual goal of 21 with this updated protocol. (Previous version had target accrual of 39 patients). This means additional 18 patients are needed to complete the study. Patients treated at 5 mg included 2 patients with recent anti-B cell therapy (Rituximab, CAR T cells) and did not develop antiQbeta antibody important for CMP001 function. We updated the exclusion criteria to account for this observation.

2.1.3 Dose-Limiting Toxicities

The DLT observation period is 15 days from date of first (W1D1) CMP-001 injection (i.e., following 3 doses of CMP-001; W1D1, W2D1, W3D1). Subjects who have received at least one dose of CMP-001 and pembrolizumab are evaluable for DLT assessments.

DLTs are defined below and only include AEs that are considered possibly, probably, or definitely related to the CMP-001 plus pembrolizumab combination. Attribution of AEs specifically to either CMP-001 or pembrolizumab is challenging, therefore, the relationship to CMP-001 should be based on attribution to the combination of the two study drugs (CMP-001 + pembrolizumab).

The following AEs will be considered DLTs **if deemed related to study drug combination**:

- Hematologic
    - Grade 4 neutropenia
    - Febrile neutropenia, defined as absolute neutrophil count (ANC) <1000/mm3 with a temperature of ≥ 38.3 degrees C
    - Grade ≥ 3 neutropenic infection
    - Grade ≥ 3 thrombocytopenia with clinically significant bleeding seeking medical intervention
    - Grade 4 thrombocytopenia
- Non-hematologic:
    - Grade ≥ 3 toxicities (non-laboratory); excluding:
        - Grade 3 fatigue lasting <7 days
        - Grade 3 arthralgia or myalgia that downgrades to less or equal to grade 2 within 3 days of supportive care
        - Grade 3 pain at injection site that downgrades to less than or equal to Grade 2 within 3 days of supportive care

        - Grade 3 electrolyte abnormalities that are asymptomatic and reversed with medical intervention within 3 days
    - Grade ≥ 3 nausea, vomiting or diarrhea despite maximal medical intervention
    - Grade 4 aspartate aminotransferase (AST) and alanine aminotransferase (ALT) unless alternate explanations such as viral hepatitis or disease progression in the liver
- Other (non- AST/ALT) non-hematologic Grade ≥ 3 laboratory value if the abnormality leads to overnight hospitalization

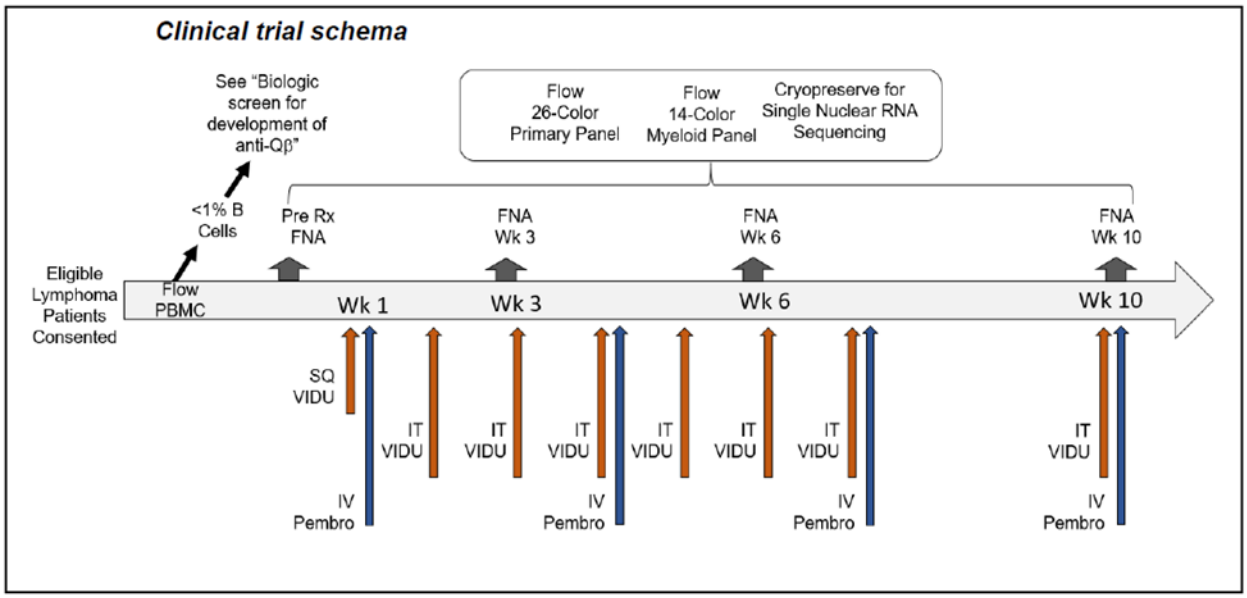
IMPORTANT: CMP-001 activates plasmacytoid dendritic cells (pDC) through agonism of TLR9. Upon activation by CMP-001, pDCs will induce large amounts of interferon and TH1-promoting cytokines. Therefore, it is expected that toxicities associated with CMP-001 dosing may resemble interferon-related toxicities as well as symptoms associated with cytokine release such as chills, rigors, fever, nausea/vomiting, flu-like symptoms and/or hypotension which may present hours after CMP-001 injection. **Therefore, AEs such as headache, chills, rigors, fever, nausea/vomiting, flu-like symptoms and/or hypotension that are <u>Grade 3 and below</u> AND resolved to Grade 1 or below within 24 hours with standard supportive care <u>will not</u> be considered a DLT.** All toxicities regardless of grade should be managed according to standards of care and reported as AEs.

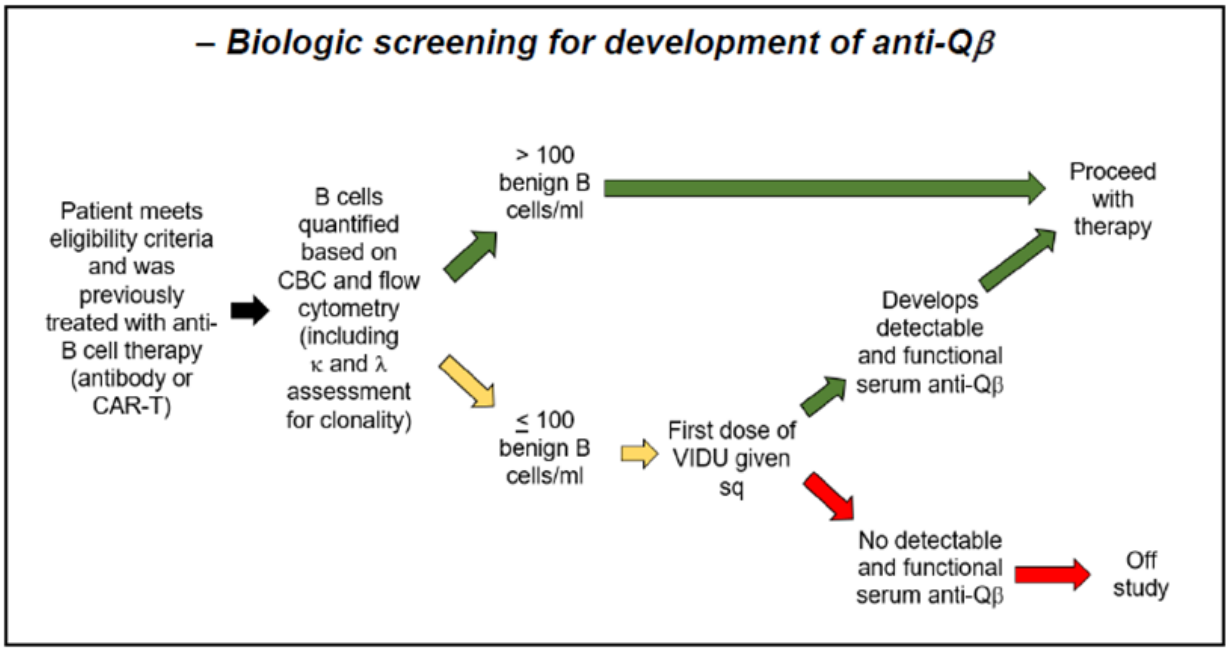
An AE believed by the Investigator to be caused by tumor flare or pseudoprogression does not necessarily need to be considered a DLT. Any such cases that would otherwise meet DLT criteria must be discussed immediately with the Medical Monitor. If the Investigator, Medical Monitor, and Sponsor agree that tumor flare is a likely explanation for the AE, treatment with CMP-001 may continue as long as the subject is closely monitored by the Investigator or study staff while on study.

Subjects who experience a DLT will have CMP-001 and pembrolizumab dosing withheld until the toxicity has returned to ≤ Grade 1. If the Investigator determines that continued treatment with CMP-001 is in the subject's best interest, treatment of CMP-001 may resume at a reduced dose, one dose level lower than the subject's current dose at the same schedule after consultation with the Sponsor. Only one dose reduction is allowed. Subjects who continue to experience DLTs must come off study. If a CMP-001 injection is delayed due to toxicity, including a DLT, it should be given as soon as possible once the toxicity has resolved.

The Investigator may escalate the subject back to the original dose level if: 1) the lower dose level was tolerated without any DLTs; 2) Sponsor approval is given.

2.2 Trial Diagram





3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective

The primary objective of the study is:

• To find the dose of CMP-001 that when given in combination with pembrolizumab in subjects with selected lymphoma results in optimal clinical efficacy and acceptable toxicity

3.2 Secondary Objective

The secondary objectives of the study are:

- To assess and describe the safety profile of CMP-001 when given in conjunction with pembrolizumab.
- To assess and describe the pharmacodynamic effects of the addition of CMP-001 to pembrolizumab on immunologic function.
- To estimate objective response rate

3.3 Exploratory Objective

Exploratory study objectives include:

• To assess changes in T cell function in response to treatment with CMP-001;

• To assess multiple parameters of immune status in the tumor microenvironment (ie, in tumor tissue) prior to starting treatment with CMP-001 and correlating these with anti-lymphoma activity observed while on study to screen for potential predictive markers; and

• To assess multiple parameters of immune status in the tumor microenvironment comparing pre- vs. post-CMP-001 samples as potential indicators of biological effect of CMP-001 on the tumor and the tumor microenvironment.

4.0 BACKGROUND & RATIONALE

4.1 Background

This phase I/II study of CMP-001 plus pembrolizumab will be conducted in subjects with lymphomas who have had stable or progressive disease following previous treatment. Although pembrolizumab has led to responses in a minority of patients with B cell lymphoma, most subjects do not achieve partial or complete responses and many of these patients ultimately experience disease progression. Additionally, there are patients with Hodgkin lymphoma that fail pembrolizumab. The purpose of this combination is to augment the immune response and improve efficacy.

CMP-001 is composed of (i) a virus-like particle comprised of capsid proteins derived from bacteriophage Qbeta, which encapsulate (ii) a cytosine linked to a guanine by a phosphate bond (CpG) oligodeoxynucleotide (ODN) known as G10, which is a Toll-like receptor 9 (TLR9) agonist designed to induce high levels of type I interferon production and an anti-tumor CD8+ T cell response through activation of TLR9 in plasmacytoid dendritic cells (pDC). The therapeutic agent is a virus like particle referred to as QbG10.

QbG10 has been previously studied in clinical trials under the name CYT003. In this protocol, the name CYT003 will refer to historical data using the product in non-oncology settings. The name CMP-001 will refer to Regeneron Pharmaceuticals' plans for the agent.

4.1.1 Preclinical and Clinical Trial Data on CMP-001

4.1.1.1 Advanced Melanoma study (NCT02680184)

Intratumoral administration of CMP-001 is currently being evaluated in combination with pembrolizumab in subjects with advanced melanoma resistant to checkpoint inhibitors.

In study CMP-001-001, A Multicenter, Open-label Phase 1b clinical Study of CMP-001 in Combination with Pembrolizumab in Subjects with Advanced Melanoma, CMP-001 is being administered IT on a weekly (Schedule A) and every 3 weeks (Q3W) (Schedule B) schedule across a dose range of 1-10 mg. To date, approximately 45 subjects have been treated in the CMP-001-001 study. Preliminary analysis of safety demonstrates an acute toxicity profile that predominantly consists of Grade 1-2 AEs associated with cytokine release including mild fever, chills, rigors, nausea, vomiting and occasional hypotension In some subjects, the severity of this AE profile is increased. These AEs typically present after the third CMP-001 dose and generally resolve within a few hours with standard supportive care. A treatment algorithm has been developed for the management of these reactions and can be found in Section 6.2.1. CMP-001-001 AE summary of the Dose Escalation Phase are presented in Table 2.

Table 2: Related AEs Reported in More than One Subject in CMP-001-001 Study

CMP001-001 Protocol Related AEs Reported in More than One Subject*		
	N (%) of Subjects	
	Schedule A^ (N=28)	Schedule B^^ (n=11)
Anemia	4 (14.3%)	-
Chills	15 (53.6%)	-
Constipation	2 (7.1%)	-
Cough	2 (7.1%)	-
Diarrhea	3 (10.7%)	-
Fatigue	7 (25.0%)	2 (18.2%)
Fever	16 (57.1%)	-
Flushing	2 (7.1%)	-
Headache	6 (21.4%)	2 (18.2%)
Hypertension	2 (7.1%)	-
Hypotension	8 (28.6%)	-
Injection Site Pain	2 (7.1%)	3 (27.3%)
Nausea	8 (28.6%)	-
Pruritus	3 (10.7%)	-
Rigors	6 (21.4%)	-
Tachycardia	2 (7.1%)	-
Vomiting	8 (28.6%)	2 (18.2%)
*Based on EDC data as of 30 May 2017 ^ Schedule A includes Cohort 1 (1 mg, n=3); Cohort 2 (3 mg, n=12); Cohort 4 (5 mg, n=6); Cohort 6 (10 mg, n=3); Cohort 8 (10 mg, n=4) ^^ Schedule B includes Cohort 3 (3 mg, n=4); Cohort 5 (5 mg, n=3); Cohort 7 (10 mg, n=3), Cohort 9 (10 mg, n=1)		

4.2 Rationale

It is hypothesized that through its TLR9-mediated immunostimulatory effects, CMP-001 will enhance the antitumor activity of anti-PD-1 antibodies.

4.2.1 Rationale for immune checkpoint blockade in lymphoma:

Therapeutics based on checkpoint blockade, including those that interrupt the PD1 axis, have created huge excitement in the field of cancer immunotherapy. There is strong biologic rationale to assess this approach in NHL. In NHL, the lymphoma cells often express PD-L1 (B. J. Chen et al., 2013; Myklebust et al., 2013) as do circulating lymphoma cells (Rossille et al., 2014). PD1 is detected on benign T cells within the NHL tumor microenvironment (Muenst, Hoeller, Willi, Dirnhofera, & Tzankov, 2010; Xerri et al., 2008). Thus, lymphoma cells expressing PD-LI provide a negative signal to PD1-expressing T cells, thereby blunting the anti-lymphoma T cell response. Preliminary results of early phase clinical trials demonstrate anti-PD1 antibodies including pembrolizumab (Merck) and nivolumab (Bristol Meyers Squibb) have activity in NHL although only a subset of NHL subjects respond. For example, phase II study of pembrolizumab as single agent in patients with CLL and B-cell NHL (MC1485, NCT02332980). Preliminary results in the eight evaluable indolent NHL patients showed 25% ORR (2PR) and 1 CR and 2 PR among

DLBCL (Ding et al. ASH 2015). UI/MC Lymphoma SPORE investigators participated in studies demonstrating nivolumab also has single agent activity in relapsed/refractory NHL with 15-40% of subjects responding depending on histology (Lesokhin et al., 2016). In relapsed DLBCL, PD1 blockade after autologous stem cell transplant resulted in ~50% overall response rate in subjects who had residual disease after transplant (Armand et al., 2013). In relapsed FL, 66% ORR and 50% CR were observed with the combination therapy of rituximab and anti-PD1 (Westin et al., 2014). Thus, PD1 blockade has clear efficacy in NHL, but there is considerable room for improvement. One potential explanation for the limited response rate of single agent anti-PD1 is the lack of lymphoma-specific T cells in some patients.

4.2.2 Rationale for Combining a TLR-9 Agonist with an Anti-PD-1 Antibody:

A variety of observations support the potential for CpG ODNs to enhance the antitumor effects of checkpoint inhibitors in general, and anti-PD-1 specifically. Despite the strong induction of cytolytic T lymphocyte (CTL) responses seen in previous human clinical trials of TLR9 agonists in oncology, very few objective responses have been seen, and the T cell responses often are not sustained, especially within tumors (Appay et al., 2006). A possible explanation for this lack of clinical efficacy is provided by the recent finding that the T cells induced following TLR9 agonist therapy in humans show very high levels of PD-1 expression (Fourcade et al., 2014). PD-1 is a "checkpoint" molecule that negatively regulates T cell function when it interacts with its ligand PD-L1, commonly expressed on tumors (D. S. Chen & Mellman, 2013). Thus, although TLR9 agonists are capable of inducing large numbers of tumor-specific CD8+ T cells in cancer patients, the expression of PD-1 on these T cells blocks their function. The addition of an anti-PD-1 antibody to CD8+ T cells from melanoma patients who had been treated with a TLR9 agonist significantly increased the T cell function for cytokine secretion (Fourcade et al., 2014), providing a strong rationale for the use of the combination of TLR9 agonists and anti-PD-1 antibodies in cancer therapy.

In a separate study, a CpG ODN (not CMP-001) in combination with anti-CTLA-4 or anti-PD-1 increased the survival of mice with MB49 bladder cancer, with anti-PD-1 plus CpG being 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 (CD25FoxP3-) CD4 splenocytes. Further, decreased levels of regulatory T cells (Tregs) were detected in the tumor area of treated animals after aCTLA-4 or aPD-1 plus CpG therapy (Mangsbo et al., 2010).

In an ovarian cancer model, mice treated with a surrogate TLR9 agonist (not CMP-001) in combination with anti-PD-1 or anti-PD-L1 antibodies also showed improved survival (Duraiswamy, Freeman, & Coukos, 2013). Yet another study was conducted in primary melanomas in *Hgf-Cdk4* R24C mice, which imitate human immune cell–poor melanomas with a poor outcome (Bald et al., 2014). This study demonstrated that treatment with immunostimulatory RNA, a TLR7 agonist with immune effects similar to the TLR9 agonist CMP-001, was associated with cytotoxic immune cell recruitment, subsequent upregulation of PD-L1 expression in tumor tissue, and an increased expression of PD-1 on peripheral blood CD8 + T cells. In this model, mice treated with the combination of TLR7 agonist RNA and anti-PD-1 antibody had significantly prolonged survival compared to control animals.

4.2.3 Rationale for Intratumoral Administration of TLR9 Agonist:

The intended mechanism of action of CMP-001 in oncology is the activation of TLR-9 in plasmacytoid dendritic ecells (pDC) within the tumor or the tumor-draining lymph nodes (tumor-associated pDC). Tumor-associated pDC activated by CMP-001 are expected to release large amounts of type I interferons (IFN), and increase their expression of costimulatory molecules and tumor antigen presentation to T-cells, culminating in the generation of a clinically effective anti-tumor T-cell response. In order for this response to be specific for the tumor, the pDC should have taken up the tumor antigens already, which requires them to be activated either within the tumor, or the draining lymph nodes, which in turn requires the intratumoral route of administration to reach a locally effective concentration of CMP-001: systemic administration of TLR-9 agonists results primarily in liver, spleen, and RES (reticuloendothelial system) uptake with little specific activation of pDC in peripheral lymph nodes. Immature tumor-associated pDC contribute to tumor growth and an adverse prognosis in cancer patients (Demoulin, Herfs, Delvenne, & Hubert, 2013; Lombardi, Khaiboullina, & Rizvanov, 2015). Activating and maturing these pDC through intratumoral administration of CMP-001 is expected to reverse the pDC functional effects from promoting to antagonizing tumor growth, and from supporting immune tolerance to inducing an anti-tumor CD8+ T cell response. Peritumoral administration is an acceptable alternate if it is impossible to perform intratumoral administration in an individual patient because peritumoral injection will still activate tumor antigen-bearing pDC in the tumor-draining lymph nodes (though not in the tumor itself which is why intratumoral administration is preferred). However, administration of CMP-001 subcutaneously in areas distant to a tumor is not expected to provide any positive signals to the tumor antigen-bearing pDC in the tumor or draining lymph nodes. In non-clinical models, intratumoral dosing is far more effective than distant subcutaneous dosing and is able to induce regression not only of the directly injected tumor lesion but also of distant metastases (Heckelsmiller et al., 2002; Shirota, Shirota, & Klinman, 2012) supporting the intended intratumoral clinical route of administration.

4.2.4 Rationale for combining anti-PD1 and CMP-001 in lymphoma:

We first evaluated the anti-tumor effects of CMP-001 injected intratumorally in combination with anti-PD1 in syngeneic, immunocompetent murine lymphoma models. In these studies, mice were inoculated bilaterally with lymphoma. Once tumor was palpable on both flanks, mice were treated with systemic anti-PD1, intratumoral CMP-001 (into the tumor on one flank only) or a combination of systemic anti-PD1 and unilateral intratumoral CMP-001. Survival and tumor growth, including growth of the tumor injected with CMP-001, and the tumor on the contralateral flank that was not injected with CMP-001, were followed. These studies demonstrated that the combination of systemic anti-PD1 and intratumoral CMP-001 induces regression of both the treated tumor and the contralateral tumor that was not treated with CMP-001. Survival of mice treated with both agents was superior to that of mice treat with either agent alone. Depletion of T cells abrogated the antitumor therapeutic effect in the injected tumor as well as the contralateral tumor (data not shown) confirming the anti-tumor effect is T cell mediated.

4.3 Justification for Dose

4.3.1 Justification for CMP-001 dosing:

The first CMP-001 injection stimulates antibody formation to the VLP of CMP-001 and will be given subcutaneously. Subsequently, CMP-001 will be administered by intratumoral injection every week for seven doses. The seventh dose (C7D1) is to be followed by booster doses given every 3 weeks.

The starting dose for CMP-001, 5 mg, was selected based upon the combination with identical pembrolizumab dosing in a Phase I/II trial of the two agents in metastatic melanoma led at the University of Iowa (NCT02680184). In the first 2 cohorts in melanoma, no DLT was seen at the 5mg dose, while biologic activity and some toxicity was seen at the 7.5 mg dose.

The highest dose considered in that study, 20 mg, is the maximum planned for consideration in CMP-001 given the current formulation.

Rationale for weekly dosing of CMP-001 for the first seven doses is supported by the following points:

- The safety of weekly dosing of up to 5 mg is well-supported by previous clinical trials of CYT003-QbG10 in non-oncology indications.

- The efficacy of weekly dosing is supported by the observation that weekly vaccination of melanoma patients with the closely related compound CYT004 (essentially CYT003-QbG10 conjugated to a tumor antigen) rapidly induced anti-tumor CD4+ and CD8+ T cell responses in the majority of subjects (Braun et al., 2012; Goldinger et al., 2012; Speiser et al., 2010). Thus, considering intratumoral administration of CMP001 as a kind of in situ vaccination, weekly dosing is also expected to induce anti-tumor immunity.

- Within a week of the initial dose, humans produce an anti-Qb antibody response adequate to provide uptake of the second dose into the target TLR-9-responsive immune cells.

- The desired Th1-like pharmacodynamic effects of CpG ODN injection persist in the draining lymph nodes of mice for more than one week (Lipford, Sparwasser, Zimmermann, Heeg, & Wagner, 2000) after a single injection; less frequent dosing may fail to sustain the desired IFN induction in the tumor microenvironment and draining lymph nodes, allowing the immune suppressive effects of the tumor to dominate.

- More frequent than weekly dosing is not expected to provide any increased efficacy, and in the study of a different TLR-9 agonist in the treatment of hepatitis C virus infection, twice weekly subcutaneous injection of CPG-ODN even appeared to induce a slightly weaker immune response in the dose given three days after previous injection compared to the dose given 4 days after previous injection (McHutchison et al., 2007).

In previous clinical trials of CYT004 and other TLR9 agonists as cancer vaccines, the anti-tumor T cell responses were detectable within 8 weeks (Braun et al., 2012; Fourcade et al., 2014), supporting the initial seven weekly intratumoral doses of CMP-001 to induce a strong anti-tumor

T cell response. Following this induction phase of therapy, the rationale for every 3-week intratumoral injections is to maintain and boost the anti-tumor response with the goal of achieving systemic control and eradication not only of the injected lesion but also distant disease.

4.3.2 Justification for Pembrolizumab dose:

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),

- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and

- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5 fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported

by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.4 Safety Endpoints

The primary safety endpoint of this study is safety and tolerability of CMP-001 when given in conjunction with pembrolizumab.

4.5 Efficacy Endpoints

The primary efficacy endpoint of this study is objective response rate of CMP-001 when combined with pembrolizumab.

4.6 Biomarker Research

Biomarker research will assess changes in T cell function in response to treatment with CMP-001. Additionally, it will assess multiple parameters of immune status in the tumor microenvironment (ie, in tumor tissue) prior to starting treatment with CMP-001 and correlating these with anti-lymphoma activity observed while on study to screen for potential predictive markers. We also plan to compare multiple parameters of immune status in the tumor microenvironment in pre- vs. post-CMP-001 samples as potential indicators of biological effect of CMP-001 on the tumor and the tumor microenvironment.

5.0 STUDY POPULATION

5.1 Participant Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Male/female participants who are at least 18 years of age on the day of signing informed consent with histologically or cytologically confirmed diagnosis of relapsed or refractory Hodgkin Lymphoma or Non-Hodgkin Lymphoma (B and T cells).

2. Male participants: A male participant must agree to use a contraception as detailed in Appendix C of this protocol during the treatment period and for at least five months after the final CMP-001 and pembrolizumab dose and refrain from donating sperm during this period.

3. Female participants: A female participant is eligible to participate if she is not pregnant (see Appendix C), not breastfeeding, and at least one of the following conditions applies:
   a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix C
   OR
   b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix C during the treatment period and for at least 5 months after the last dose of study treatment.

4. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial prior to the initiation of any study procedures. The participant must be capable of understanding and complying with protocol requirements.

5. Have measurable disease based on Cheson 2007 (Cheson et al., 2007). Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

6. Subjects must have at least one tumor lesion with a longest diameter of ≥ 1 cm that can be easily palpated or detected by ultrasound to facilitate intratumoral injection of CMP-001 (eg, tumor in skin, muscle, subcutaneous tissue or accessible lymph node).

7. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Evaluation of ECOG is to be performed within 7 days prior to the date of allocation/randomization.

8. Patients previously treated with anti B cell directed therapy, such as anti-B cell antibody therapy within the past year or a history of CAR T therapy at any time, will be evaluated for the presence of B cells by flow cytometry on peripheral blood. Patients with > 100 benign B cells will be considered eligible. Those with ≤ 100 benign B cells may still be enrolled at the investigator's discretion but will only proceed to the therapeutic phase of the study if they have been shown to generate an anti-Qbeta antibody response, as demonstrated by ELISA assay, in response to the priming dose of vidutolimod. (Trial Schema, section 2.2)

5.2 Participant Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. A WOCBP who has a positive urine pregnancy test within 72 hours prior to first dose of study drug. (see Appendix C). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
2. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137) within 4 weeks of enrollment into this trial.

3. Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks or within 5 half-lives, whichever is shorter, prior to first dose of study drug.

   Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible.

   Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.

4. Has received prior radiotherapy within 2 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

5. Has received a live vaccine or live-attenuated vaccine within 30 days prior to the first dose of study drug. Administration of killed vaccines is allowed.

6. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks, or within 5 half-lives, whichever is shorter, prior to the first dose of study treatment.
   Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks, or 5 half-lives, whichever is shorter, after the last dose of the previous investigational agent.

7. Has a diagnosis of primary immunodeficiency disorder or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

8. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

9. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e. without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.

10. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

11. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

12. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.

13. Has an active infection requiring systemic therapy.

14. Has a known history of Human Immunodeficiency Virus (HIV). Note: No HIV testing is required unless mandated by local health authority.

15. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA is detected) infection. Note: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

16. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

17. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

18. Patients with allotransplant in past 5 years or those with evidence of graft vs. host disease (GVHD) will be excluded.

19. Have inadequate organ function as defined in the following table (Table 3). Specimens must be collected within 10 days prior to the start of study treatment.

Table 3 Adequate Organ Function Laboratory Values

System	**Laboratory Value**
Hematological	
Absolute neutrophil count (ANC)	≥500/µL [a, b]
Platelets	≥50,000/µL [a, b]
Hemoglobin	≥8 g/dL [a, b]
Renal	
Creatinine OR Measured or calculated [c] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN

AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal. [a]Growth factor and/or transfusion support is permissible to stabilize participant prior to study treatment if needed. [b]No lower limit if cytopenia is related to bone marrow involvement. [c]Creatinine clearance (CrCl) should be calculated per institutional standard. Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.	

5.3 Lifestyle Restrictions

5.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.3.2 Contraception

Pembrolizumab or CMP-001 may have adverse effects on a fetus in utero. Refer to Appendix C for approved methods of contraception.

For this study, male participants will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

5.3.3 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study treatment. The site will contact the

participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck within 2 working days if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to Merck and followed as described in Section 8.2.2.

5.3.4 Use in Nursing Women

It is unknown whether pembrolizumab or CMP-001 is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breast-feeding are not eligible for enrollment.

5.4 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician.

5.4.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 8.2.

5.4.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab and CMP-001

- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion. CMP-001 in this case must be suspended until radiation treatment is completed.
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.4.3 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.2.2, [Table 7]. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab or CMP-001.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab or CMP-001, the Investigator does not need to follow the treatment guidance. Refer to [Table 7] in Section 6.2.2 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

5.5 Participant Withdrawal/Discontinuation Criteria

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 8.1.6 – Other Procedures.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment
- Confirmed radiographic disease progression as per Cheson 2007 criteria if accompanied by medically significant clinical deterioration, in the judgment of investigator. (Continuation of treatment through suspected pseudo-progression is permitted).
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Unacceptable adverse experiences as described in Section 6.2.2.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test
- Noncompliance with study treatment or procedure requirements
- Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 every 3 week doses of Pembrolizumab beyond the date when the initial CR was declared.
- The participant is lost to follow-up
- Completion of 35 treatments (approximately 2 years) with pembrolizumab

Note: The number of treatments is calculated starting with the first dose.

- Administrative reasons

Subjects discontinuing study treatment earlier than planned or withdrawing from the study should undergo the End of Treatment (EOT) clinical and laboratory assessments (see Section 7.0 TRIAL FLOW CHART) as soon as possible after study treatment is stopped. The required 30 day follow-up phone call should also be completed. The reason for withdrawal will be recorded in the electronic case report form (eCRF) and the subject's source medical record.

If a subject withdraws from the study prior to completion of the 21 day assessment period for a reason other than a DLT, then a replacement subject will be enrolled at that dose level.

5.6 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to participants as detailed in section 6.2

4. Plans to modify or discontinue the development of the study drug

In the event of Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to participant treatment can be made.

6.0 TREATMENT OF SUBJECTS

6.1 Study Drug Administration

6.1.1 Recommended Prophylaxis Before and After CMP001 Dosing

To reduce the incidence and severity of symptoms associated with CMP-001 administration, prophylaxis is required. All recommended prophylaxis should be administered before initiation of the CMP-001 injection. The medications are recommended for oral administration, but IV is acceptable at the discretion of the Investigator. There is no waiting period between the end of prophylaxis and the start of the CMP-001 injection. The optimal recommended regimen that has been effective for the treatment of CMP-001 associated AEs, should include all the following components:

- Intravenous fluids (eg, approximately 1000 cc IV normal saline)
- Antipyretics (eg, acetaminophen 1000 mg and a non-steroidal anti-inflammatory agent such as indomethacin 50 mg or ibuprofen 600 to 800 mg)
- Anti-emetics (eg, ondansetron 8 mg)
- Antihistamine: (diphenhydramine 50 mg, with or without an H2-antagonist)
- Recommended: hydrocortisone 25 mg at the investigator's discretion.

Subjects with a history of adrenal insufficiency are at increased risk for moderate to severe AEs such as hypotension. It is strongly recommended that these subjects receive stress dose steroids

(eg, 50 to 100 mg hydrocortisone orally every 8 hours) before and for 24 to 48 hours after each CMP-001 injection.

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.

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

6.1.2 Administration of CMP-001

If possible, the full volume should be injected into a single progressing lesion and as appropriate for the subject's dose cohort. If the full volume cannot be injected within the tumor, then the remaining drug volume should be injected into a second accessible tumor, if present. If the full volume still cannot be administered into the tumor then peritumoral injection of any remaining volume is acceptable.

If over time an injected tumor is clearly responding to therapy (eg, regresses below the minimum size that can readily be injected with the required volume), or if in the judgment of the Investigator, the subject cannot tolerate continued injections in that lesion because of local injection site reaction or other issues, then the injection may instead be administered intratumorally into a different progressing tumor lesion, or peritumorally at the original site or at a new tumor lesion.

If a single lesion is the only injectable lesion and decreases or disappears over time, we plan to continue injecting into the tumor bed for the entire 7 weeks (+) course of treatment and until first radiological assessment. If after the first radiological assessment at week 7, there is no tumor site available for injection, we plan to continue with Pembrolizumab +/- injection to tumor bed until progression, toxicity or if in the investigator's opinion continued treatment is in subject's best interest.

CMP-001 should be injected using aseptic technique. Use of topical and/or local anesthetic is permitted. For administration of CMP-001 a single cutaneous insertion point should be used and multiple needle tracks within the tumor should be injected until the full volume has been instilled.

The information on dose, volumes, and numbers of sites injected will be recorded for analysis.

6.1.2.1 Goals for Injection

The clinical goal of intratumoral therapy with CMP-001 is to induce a systemic CTL response that eradicates the injected tumor and distant metastases. The direct immunologic goals of intratumoral therapy are: i) to alter the tumor microenvironment in a Th1 manner by inducing the production of type I IFN by tumor infiltrating pDC (AKA IFN-producing cells) through TLR9; ii) to trigger the maturation of tumor-infiltrating pDC from an immature tumor-protective phenotype to a mature, anti-tumor CTL inducer; and iii) to alter the tumor draining

lymph node microenvironment in a Th1 manner.

Intratumoral injection is required to achieve the first goal, but either intratumoral or peritumoral injection can achieve the second goal: in both cases the injected CMP-001 traffics via lymphatics to draining lymph nodes (DLNs) where it activates resident pDC inducing a Th1-like cytokine/chemokine milieu within the tumor-draining lymph nodes. In addition, some tumor- infiltrating pDC also may mature and migrate from the tumor into the DLN following TLR9 activation from intratumoral CMP-001 injection. For these reasons, peritumoral injection is permitted whenever the entire dose cannot be injected into the selected tumor(s).

6.1.2.2 Tumor Selection

Tumors selected for CMP-001 intratumoral injection should be at least 0.5 cm in diameter and may be cutaneous, subcutaneous, and/or nodal tumors that are visible, palpable, or detectable by ultrasound guidance; visceral tumors are not injected. Patient candidates for CMP-001 injection may have more than one accessible tumor as a candidate for intratumoral injection. The most preferred of these to be selected for injection is the most aggressively progressing tumor in the judgment of the Investigator. Such tumors may have additional mutations compared to non- progressing tumors, and perhaps express neoantigens that may be particularly good targets for the induction of a therapeutic immune response. Tumors that are already regressing are not preferred for injection because they are believed to already have a tumor microenvironment supporting immune rejection, and there may be less additional benefit to CMP-001 injection compared to selecting progressing or stable tumors. When several progressing tumors are available for injection, the Investigator should select the one that is most amenable to injection (eg, the most superficial) and/or the tumor that is the smallest capable of receiving the entire volume of CMP-001 to be delivered (see Table 4). The rationale for selecting the smallest appropriate tumor is to have the highest possible intratumoral concentration of CMP-001, which is expected to maximize the induction of a Th1-like tumor microenvironment.

6.1.2.3 Dosage and Regimen

All subjects to be treated with CMP-001 must have at least one such appropriate tumor for CMP-001 injection (eg, tumor in skin, subcutaneous tissue or accessible lymph node).

At Screening, the selected tumor(s) must be large enough to allow intratumoral injection of the intended volume of CMP-001 (Table 4; Table 5). If possible, the entire dose volume should be injected into a single tumor. The tumor selected for injection need not be the largest lesion. If the subject has no single tumor large enough to allow injection of the entire volume of CMP-001, then the volume may be split among 2 or more smaller lesions. However, the minimal number of lesions should be chosen to allow injection of the entire volume, instead of splitting the dose among a larger number of smaller lesions. The same tumor(s) should be injected each week during therapy, if possible, except as outlined below to involuting tumors.

Dosing of CMP-001 is intended to be given weekly for seven weeks (and then at 3-week intervals for the duration of treatment). To assure maximum effectiveness, consecutive doses

of CMP-001 should always be administered at least 96 hours apart.

6.1.2.4 Dividing the CMP-001 Dose between Two or More Tumors

It is preferred to inject the entire CMP-001 dose into a single progressing tumor that is amenable to injection if one of the appropriate size for the entire volume is available (Table 4). If no single progressing tumor is large enough, then the dose should be split between one or more smaller progressing tumors, or a smaller progressing tumor and one or more non-progressing tumors.

6.1.2.5 Changing the Selected Tumor

Therapy of a selected lesion generally should continue per protocol unless the tumor is dramatically responding clinically through involution. Inflammation of the injected tumor is expected following the 2nd and subsequent injections but should not be mistaken for a clinically effective anti-tumor response. It is expected that injection of the selected lesion may need to be continued for the full 7 weekly doses to maintain the Th1-like cytokine/chemokine milieu for long enough to drive an effective CTL response before a clinical response may be apparent, and that continued injections every 3 weeks may be required to maintain the Th1 effects for maximal achievable clinical response. If during therapy the injected tumor is clearly involuting and shrinking, and if a different eligible accessible tumor is progressing, then the Investigator should change the selection to the progressing tumor, injecting the full or maximal feasible dose (as outlined in Table 4) of CMP-001 into that tumor(s), and continuing to inject the new tumor(s) until the end of the study (or that tumor shows involution, in which case a third progressing tumor may be selected).

Table 4: Selection of CMP-001 Injection Volume Based on Lesion Size

Lesion Size (Longest Dimension)	CMP-001 Injection Volume[1]
>0.5 to 1.5 cm	Up to 0.5 mL
>1.5 to 2.5 cm	Up to 1 mL
>2.5 to 3.5 cm	Up to 2 mL
>3.5 to 5 cm	Up to 3 mL
> 5 cm	Up to 4 mL

[1]: These volumes are intended only as a guideline to the Investigator of what may be injected for tumors in a particular size range. If the Investigator has selected a tumor for injection and is unable to deliver the intended intratumoral volume because of patient pain or other factors, then the remainder of the dose may instead be injected peritumorally.

Table 5: CMP-001 Injection Volumes

Dose Cohort	Volume to be injected for 1mg/mL Concentration	Volume to be Injected for 5 mg/mL concentration
7.5 mg	7.5 mL	1.5 mL
10 mg	10.0 mL	2 mL

6.1.2.6 Procedure of CMP-001 Administration

Topical or local anesthesia may be performed as appropriate in the Investigators' judgment. Using standard aseptic technique, the needle is inserted near the tumor periphery (Figure 1, left panel) and is advanced into the tumor to the desired depth (usually to the needle hub, if the tumor size permits) while maintaining gentle backward pressure on the syringe plunger to confirm extravascular location of the needle tip. The syringe and needle are then 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 1, middle panel). With the tip of the needle still within the skin, the syringe is then rotated by ~20-40^{o} and the process of insertion and injection during needle withdrawal is repeated (Figure 1, right panel). Using this process, CMP-001 is injected along multiple tracks through a single insertion point as far as the radial reach of the needle allows within the tumor; two insertion points can be used if the tumor is larger than the radial reach of the needle and the intended CMP-001 volume cannot be delivered from 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.

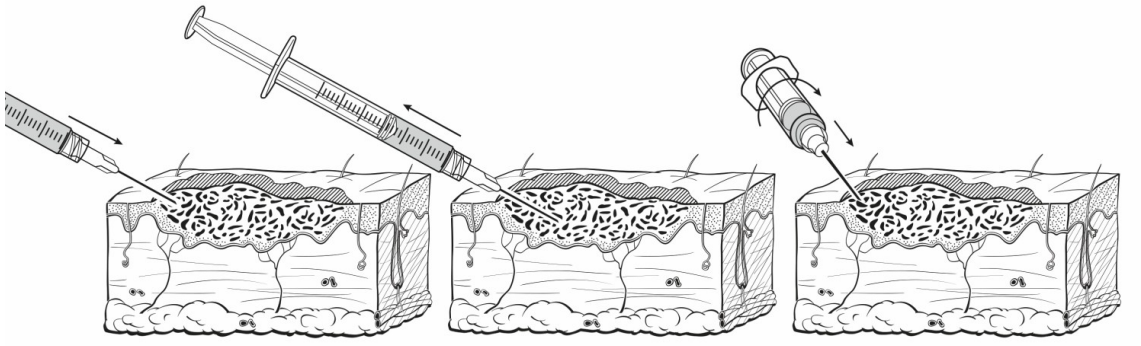


Figure 1: Method for CMP-001 Intratumoral Injection

Essentially the same process is performed for cutaneous, subcutaneous, and nodal injections, but for deeper injections, the tip of the needle may be kept within the tumor and a longer needle may be used.

Injections will be performed by Oncologist if easily accessible lesions or by interventional radiologist for lesions that need image guidance for injections. Interventional radiologist will be sub-investigators on this study. This is based on our experience on other trials that required injection of drug directly into tumors.

6.1.2.7 Observation Period Following CMP-001 Dosing

Following the first 5 doses of CMP-001 (W1D1, W2D1, W3D1, W4D1, W5D1), subjects must be observed for a period of at least four hours for signs and symptoms of reactions to the CMP-001 injection and other AEs.

Based upon the discretion of the Investigator, observation periods can be reduced to one hour for individual subjects who demonstrate mild to no AEs post CMP-001 injection for the first 5 doses. Reduced observation periods can be implemented starting with the 6th dose of CMP-001 (W6D1).

6.1.3 Administration of Pembrolizumab

Pembrolizumab (KEYTRUDA) is to be administered at a dose of 200 mg fixed dose administered as an IV infusion over 30 minutes every 3 weeks as per label instruction.

Table 6 Pembrolizumab Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental

6.2 Dose Modifications and Management of Study-Drug Associated Adverse Events

The following sections provide guidance on the management of toxicities that may be associated with CMP-001 and pembrolizumab. In most cases management of toxicity may require either a temporary or permanent discontinuation of both CMP-001 and pembrolizumab. However, if in the opinion of the investigator, a toxicity is more clearly related to one drug, the administration of that drug may be modified with PI consultation and approval. If a subject develops moderate to severe toxicity with CMP-001, we will consider stress dose steroids prior to subsequent CMP-001 doses.

6.2.1 CMP-001 Associated Adverse Events (see Table 2)

The safety profile for intratumoral CMP-001 in combination with Pembrolizumab has been reported in melanoma clinical trial (N=159) and treatment related adverse events described in detail in Invetigator Brochure version 07 (26July2021). Allergic reactions of an immediate type, including anaphylaxis, have been observed after CMP-001 administration. Investigators must be vigilant in identifying and managing these disorders according to institutional guidelines.

6.2.1.1 Injection Site Reactions

If subjects develop inflammation at the injection site this may be managed using cold compresses and/or acetaminophen or non-steroidal anti-inflammatory agents. If flu-like symptoms (i.e., fever, myalgia, and headache) arise, these may be managed using acetaminophen or non-steroidal anti-inflammatory agents.

6.2.1.2 Prophylaxis and Treatment of Adverse Events Associated with CMP-001

CMP-001 is designed to specifically activate TLR9, which is expressed in the endosomes of pDCs. Upon activation through TLR9, pDCs secrete cytokines, including type I IFNs and associated Th1-promoting cytokines. Given this mechanism of action, it is expected that the AE profile associated with CMP-001 administration may be similar to that seen after administration of IFNs (eg, flu-like symptoms such as fever and headaches). The recommended algorithm for the treatment of AEs associated with CMP-001 **(Figure 2)** is currently being studied in Regeneron-sponsored studies. The first line of treatment for hypotension unresponsive to supportive care such as fluids, is stress dose steroids. Additional treatment measures may include the use of drugs targeting specific cytokines believed to be involved in the development of cytokine release syndrome associated hypotension.

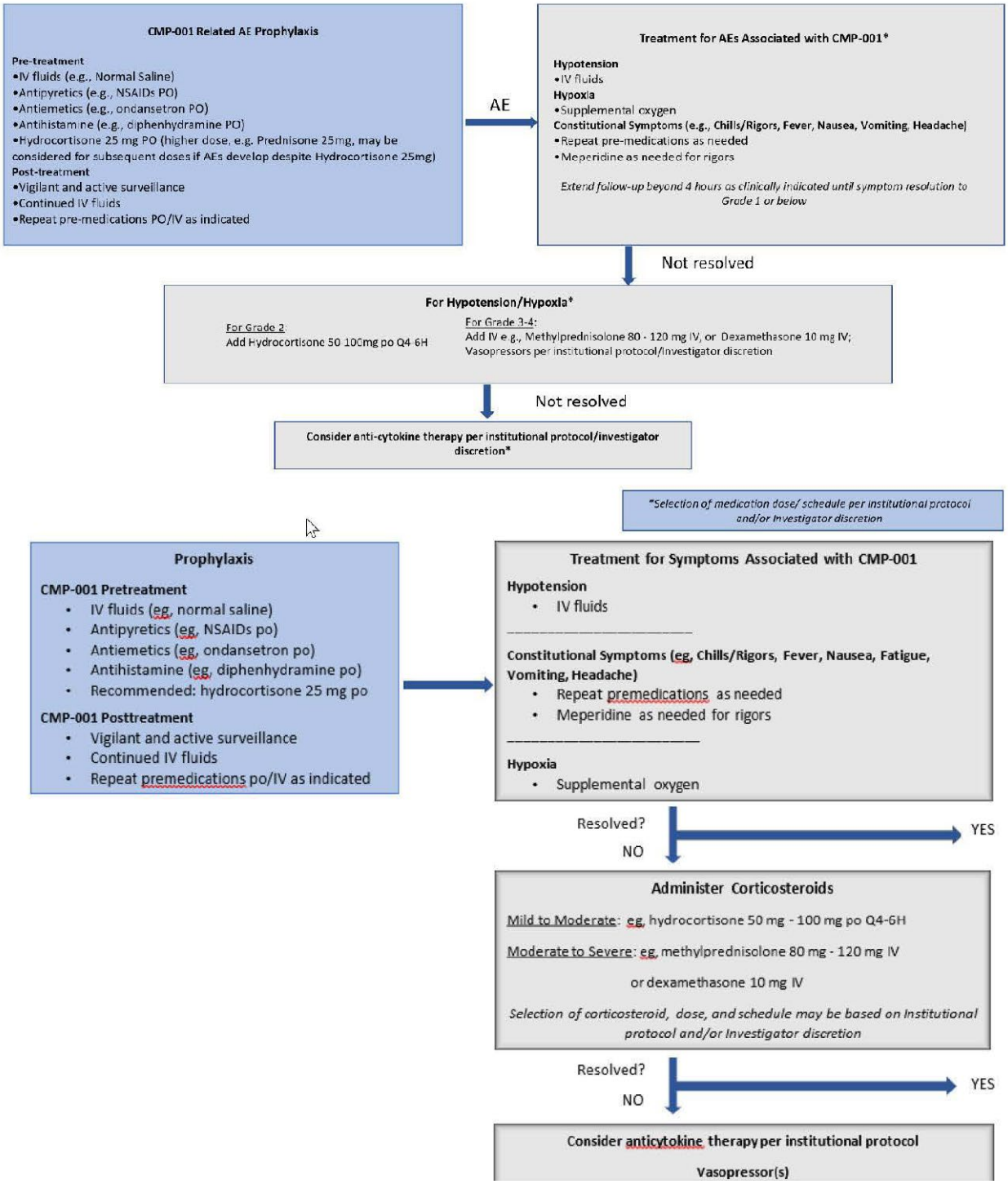


Figure 2: Recommended Treatment Algorithm for Cytokine Release Symptoms

6.2.2 Pembrolizumab-Associated Adverse Events

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 7.

Table 7 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab monotherapy and IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If study intervention has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
	Grade 2	Withhold		• Monitor changes of renal function

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

6.2.2.1 Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 8.

Table 8 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of Pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

7.0 TRIAL FLOW CHART

Procedure or Assessment	Screening (Day -21 to -1) [a]	W1 D1	W2 D1	W3 D1	W4 D1	W5 D1	W6 D1	W7 D1	W10 D1	Every 3 Weeks Post W10 (W13, W16 etc.)	End of Treatment [b]	30 Day Follow up visit [n]	Long Term Survival Follow-up[O]
CMP-001 Dose Number	n/a	1	2	3	4	5	6	7	8	9+	n/a	n/a	n/a
Visit Windows	n/a	n/a	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±7 days	±7 days	±7 days	±7 days	± 1 month
Informed Consent	X												
Eligibility Criteria Assessment	X												
Medical History, Demographics, Cancer History including Prior Cancer Medications	X												
Physical Exam [c]	X	X		X	X			X	X	X	X		
Vital Signs [d]	X	X	X	X	X	X	X	X	X	X	X		
ECOG Performance Status	X	X		X	X			X	X	X	X		
Body Weight	X	X			X			X	X	X	X		
Height	X												
Electrocardiogram (ECG) [e]	X	X		X				X			X		
Autoimmune lab panel [f]	X										X		
Clinical Laboratory Tests (hematology, serum chemistry, urinalysis) [g]	X	X	X	X	X	X	X	X	X	X	X		
Coagulation Tests (PTT & INR) [h]		X						X	X	X			
Thyroid Function Tests	X			X				X			X		
Research blood Samples [l]	X	X		X			X		X	-			
Tumor Biopsy [j]	X			X			X		X	-			
Urine Pregnancy Test [k]	X	X			X			X	X	X	X		
Disease Assessment (PET-CT/CT) [a, l]	X	At W7D1 (or two cycles) and then as clinically indicated											
Adverse Event Monitoring [n]		Assessed continually from W1D1 through EOT +30 days											
Concomitant Medications		Assessed continually from 28 days prior to first CMP-001 dose through EOT +30 days											
CMP-001 dosing [m]		X	X	X	X	X	X	X	X	X			
Pembrolizumab Dosing			Pembrolizumab will be given according to pembrolizumab label (every 3 week)										

Footnotes for Trial Flow Sheet:

a. Computed tomography (CT neck/chest/abdomen/pelvis with contrast) or PET-CT scans may be performed ≤3 weeks prior to first CMP-001 dose but up to 4 weeks will be acceptable. MRI will only be considered in specific situation if needed.

b. End-of-treatment (EOT) assessments to be performed within 7 days following removal of subject from CMP-001 treatment. Removal of a subject from CMP-001 treatment is defined as the time in which the Investigator decides to discontinue CMP-001 treatment for a subject.

c. A full physical exam will be conducted at Screening and EOT. The Screening physical exam may be performed up to 72 hours prior to the Week 1 Day 1 (W1D1) visit. If the full physical exam is performed >72 hours prior to the W1D1 visit, then a brief (symptom directed) physical exam must be performed within 72 hours prior to initiation of CMP-001.

d. For the first five CMP-001 dosing visits, vital signs are to be collected prior to CMP-001 dosing, and at 30 (±15) minute intervals for 4 hours post end of CMP-001 dosing. Based upon the discretion of the Investigator, observation periods can be reduced to 1 hour for individual subjects who demonstrate mild to no adverse events. Reduced observation periods can be implemented only after the 6th dose of CMP-001. Vital signs should be performed prior to collection of clinical laboratory tests when they are performed at the same visit. On days that CMP-001 and Pembrolizumab are both given, vital signs should be collected following the administration of CMP-001. When CMP-001 intratumoral injection and pembrolizumab dosing fall on the same day, it is recommended that CMP-001 intratumoral injection precede pembrolizumab dosing.

e. Electrocardiograms (ECGs) should be obtained at Screening and prior to CMP-001 intratumoral injection at the 1st, 3rd, and 7th CMP-001 injection (on W1D1, W3D1, W7D1), and EOT visit.

f. Autoimmune lab panel to be collected at Screening and EOT. Table 9

g. Clinical laboratory tests may be performed up to 72 hours prior to administration of CMP-001.

h. Partial thromboplastin time (PTT) and international normalized ratio (INR) tests should be obtained, and results reviewed as per schedule above. These may be obtained up to 72 hours prior to administration of CMP-001.

i. Blood samples (20 ml) for research including exploratory biomarker, immunogenicity studies, and assessment of pharmacodynamics are to be collected at screening and then on following days and times:

Blood draw pre-treatment W1D1 or before, W3D1, W6D1, W10D1 prior to dosing with CMP-001 – Additional blood draw with subsequent cycles may be requested.

j. Archival tumor samples should be identified at Screening, if available for potential access later. Additional tumor biopsies are optional and may be collected at other times then specified below at the discretion of the Investigator. Optional tumor biopsies (fresh frozen when feasible and typically FNA), will be collected prior to starting treatment on W1D1, W3D1, W6D1, W10D1. If pre-treatment biopsy prior to W1D1 treatment not done, it can be scheduled with W2D1 intra-tumor injection.

k. In women of childbearing age, Urine pregnancy testing should be performed at Screening and prior to 1st CMP-001 injection (W1D1), prior to 4th CMP-001 injection (W4D1), prior to 7th CMP-001 injection (W7D1), followed by every 3 weeks prior to treatment and EOT. A negative test within 72 hours of treatment is acceptable.

l. CT neck/chest/abdomen/pelvis with contrast or PET-CT scans to assess response will be at W7D1 (or after two cycles) and then as clinically indicated. Subjects may be asked to provide historical scans (scans performed prior to Screening) for informational purposes prior to starting CMP-001 therapy, if available.

m. The first CMP-001 injection stimulates antibody formation to the VLP of CMP-001 and will be given subcutaneously. Subsequently, CMP-001 should be administered as close to the tumor as possible if intratumoral injection not possible. A window of ± 2 day is permitted for the CMP-001 dose schedule for the first weekly CMP-001 injections and a window of ±7 days is permitted for every 3 week CMP-001 injections. To assure maximum effectiveness, consecutive IT injections of CMP-001 should always be administered at least 96 hours apart. No CMP-001 dose should be skipped. If a CMP-001 dose needs to be delayed due to toxicity the dose should be completed as soon as the toxicity has resolved.

n. The 30-Day Follow-up (+7 Days) or before new treatment is started is a safety follow up visit that may be conducted in the study clinic OR via phone. The subject should be questioned for any new AEs or ConMeds, no other safety assessments are required unless the Investigator identifies a new safety concern that requires further follow-up. This visit should occur 30 days (+7) after the EOT visit. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment, whichever comes first should also be followed and recorded.

o. All subjects will be followed for survival for 2 years (3 ± 1 month). Survival follow up may be accomplished by visit or phone contact for two years or until subject death, subject consent is withdrawn, subject is lost to follow up or the study is completed.

8.0 TRIAL PROCEDURES

8.1 Trial Procedures

The Trial Flow Chart - Section 7.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

8.1.1 Administrative Procedures

8.1.1.1 Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB/ERC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

8.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the trial.

8.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

8.1.1.4 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the trial. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

8.1.1.5 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 8.2.

8.1.1.6 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

8.1.1.7 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

8.1.1.8 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 days Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up.

8.1.1.9 Assignment of Screening Number

During the Screening process, each potential subject will be assigned a Screening Identification (ID) and once enrolled each subject will be assigned a unique Subject ID number. This number will be recorded on the subject's eCRF pages and used to identify the subject throughout the study. Once any subject number is assigned, it cannot be reassigned to any other subject. Screening ID will be assigned sequentially and PI will assign the subject ID once patient is enrolled on the study.

Subjects will be assigned to a dose level based on the sequence in which they are screened and meet eligibility criteria relative to the availability of enrollment needs.

8.1.1.10 Assignment of Randomization Number

This is an open-label study.

8.1.1.11 Trial Compliance (Medication/Diet/Activity/Other)

Dosing of CMP-001 is by intratumoral injections, and is done at the study site, by qualified site personnel. Any deviations in planned dosing will be documented in the source documents and eCRF.

8.1.2 Clinical Procedures/Assessments

8.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart 7.0 and more frequently if clinically indicated. Adverse experiences will be graded and recorded according to NCI CTCAE Version 4.0 (see Appendix B). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 8.2 for detailed information regarding the assessment and recording of AEs.

8.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

8.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

8.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 7.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

8.1.2.5 Electrocardiogram

A single standard, 12-lead ECG will be obtained as per schedule in Trial Flow Chart 7.0. Assessed ECG parameters will include heart rate and PR, QRS, QT, and QT corrected for heart rate (QTc) intervals. QT will be corrected using Bazett's (QTcB) or Fridericia's (QTcF) formula.

The ECG results will be interpreted locally at the site by a delegated medically qualified person. If indicated, ECG findings may be confirmed by a cardiologist or internist.

8.1.2.6 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix A) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart, Section 7.

8.1.3 Response/Efficacy Assessments

Disease status will be assessed by CT or PET-CT scans. Calipers may be used to measure superficial cutaneous tumors. Scans will be obtained at Screening and on follow up as per Trial Flow Chart, Section 7. These can be performed up to five days prior to starting the next cycle of therapy. The assessment method used at Screening (baseline value) to determine disease status/progression (CT vs. PET-CT) should be used throughout the course of the study if possible.

Antitumor activity will be described as ORR using Cheson 2007.(Cheson et al., 2007) For detail refer to Appendix D. Other secondary endpoints that will be assessed include complete response (CR), progression-free survival (PFS), best overall response (BOR), time to response (TTR), stable disease (SD) and duration of response (DOR).

8.1.4 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 9.

Table 9 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		Autoimmune lab panel (anti-dsDNA, ANA, ANCA, RF, and anti- RNP)
	Calcium		
	Chloride		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

‡ If considered standard of care in your region.

8.1.4.1 Pregnancy Testing

At Screening, a pregnancy test will be performed on females of childbearing potential, using a dipstick urine test by site personnel. If positive, the test will be confirmed with a serum sample (the same sample submitted for chemistry panel). If a serum pregnancy test is required, pregnancy test results must be confirmed to be negative in order for the subject to be considered eligible for inclusion in the study.

Urine pregnancy tests will also be performed for females of childbearing potential as described in Trial Flow Chart (Section 7.0).

8.1.4.2 Immunogenicity

Plasma will be assayed for the presence of anti-pembrolizumab and anti-Qbeta capsid protein antibodies as per Trial Flow Chart, 7.0.

8.1.5 Exploratory Biomarker Sampling

8.1.5.1 Blood Biomarkers

Blood samples will be assayed for immunologic studies as per Trial Flow Chart, 7.0. Sample will be assayed for 25 cytokines and chemokines. Blood samples will be collected and processed in Dr. Weiner's lab.

8.1.5.2 Biomarkers in Tumor Tissue

At Screening, tissue samples (archival tissue or biopsies) will be assayed for Immunoscore (including PD-L1 status) or another multiparameter assessment. Archival tissue should be obtained for Immunoscore (including PD-L1 status) assessment if available. If tumor PD-L1 status has been obtained prior to study entry then this value should be recorded in the eCRF.

Tumor biopsies are not mandatory and require additional informed consent for the procedure(s).

Intra-subject changes in immune status from pre- to post-treatment may be evaluated using optional tumor biopsies (fresh frozen or single cell suspension), collected prior to starting treatment and at $\geq$4 weeks after initiation of weekly CMP-001 treatment, and evaluated using Analysis of Immunoscore or other multi-parameter assessment of the tumor microenvironment.

Descriptive exploratory statistical analyses will be conducted to assess two possible relationships: 1) Baseline measures of tumor biomarkers relative to clinical outcomes for antitumor activity and 2) Change in tumor biomarkers from baseline (pre-treatment with CMP-001) to on-treatment or post-treatment with CMP-001 as an indication of pharmacodynamic effects.

8.1.5.3 Assessment of Pharmacodynamics

Elevation of IP-10 is a biomarker of the activity of type I and II interferons, which are expected to be induced by treatment with CMP-001.

Blood samples will be obtained for assessment of concentrations of the chemokine IP-10 as per Trial Flow Chart, 7.0.

8.1.6 Other Procedures

8.1.6.1 Withdrawal/Discontinuation

When a participant discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.2 - Assessing and Recording Adverse Events. Participants who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment. After discontinuing treatment following assessment of CR, these participants should return to the site for a Safety Follow-up Visit (described in Section 8.1.7.4) and then proceed to the Follow-Up Period of the study (described in Section 8.1.7.5).

8.1.6.2 Blinding/Unblinding

Open labeled study

8.1.7 Visit Requirements

Visit requirements are outlined in Section 7.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 8.0 - Trial Procedures.

8.1.7.1 Screening

As described in Trial Flow Chart, Section 7.0

8.1.7.1.1 Screening Period

As described in Trial Flow Chart, Section 7.0

8.1.7.2 Treatment Period

As described in Trial Flow Chart, Section 7.

8.1.7.3 Post-Treatment Visits

As described in Trial Flow Chart, Section 7.

8.1.7.4 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Participants with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. SAEs that occur within 90 days

of the end of treatment or before initiation of a new anti-cancer treatment, whichever comes first should also be followed and recorded.

8.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

● All AEs from Week 1 Day 1 (treatment initiation) through 30 days following cessation of study treatment must be reported by the investigator.

● All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.

● All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.

● Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately by the investigator if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at

any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify Merck.

8.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck

For purposes of this study, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

8.2.2 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

Although pregnancy and infant exposure during breast feeding are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a participant (spontaneously reported to them) that occurs during the study.

Pregnancies and infant exposures during breastfeeding that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the participant to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and infant exposures during breastfeeding that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

8.2.3 Immediate Reporting of Adverse Events to the Sponsor and to Merck

8.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is another important medical event?

- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Refer to **Table 10** for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any participant must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to Merck Global Safety.

All participants with serious adverse events must be followed up for outcome.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215-661-6229) at the time of submission to FDA.

8.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any participant must be reported within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 2 working days to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 8.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

> *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

8.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 10 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the participant, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of participant taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to Merck within 2 working days..	

	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause Merck product to be discontinued?	
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the participant was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the participant re-exposed to Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).**	
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.	
No, there is not a reasonable possibility of Merck product relationship	Participant did not receive the Merck product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a participant with overdose without an associated AE.)	

8.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

9.0 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

Data analyses will be primarily descriptive in nature. Descriptive statistics will be presented for safety, pharmacodynamic, and exploratory endpoints. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data, if applicable) of the parameter will be presented. For continuous variables, data will be presented as number (n), mean, median, standard deviation, and range (minimum and maximum). Discrete variables will be presented as frequencies or proportions. No formal statistical comparisons between dose groups will be performed. Data from all investigational sites will be pooled in the summary tables and analyses. Data collected on patients who are screen failures will not be included in any summary tables, listings, or 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.

9.2 Efficacy and Toxicity Analysis

The primary statistical analysis is based on the Bayesian optimal interval design (BOIN12) of Lin et al. (Lin et al., 2020). An adaptive escalation schema (see Section 2.1.2) is used to find a dose with optimal clinical efficacy and acceptable toxicity. The design has a minimum sample size of 3 patients and a maximum of 21. The operating characteristics of the design were estimated from 10,000 trials simulated with the BOIN12 shiny app (V1.5.2.0) available at http://www.trialdesign.org. True efficacy rate of 0.50 and toxicity rates 0.30 or lower are deemed to be clinically desirable. Efficacy of 0.10 or less is uninteresting clinically. The trial design has 36% and 49% probabilities (85% total power, 15.6 expected number of patients treated) of selecting dose 7.5 mg or 10 mg if their efficacy rates are 0.40 and 0.50, respectively, and their toxicity rates are both 0.20. The selection probabilities decrease to 70%, 47%, and 24% at higher toxicity rates of 0.30, 0.40, and 0.50. Conversely, the design has a total selection probability of 3% (type I error, 7.9 expected number of treated patients) at efficacy rates of 0.10 and toxicity rates of 0.20. Selection probabilities and expected numbers of treated patients for these and other true efficacy and toxicity rate scenarios are summarized in Table B of APPENDIX F.

9.3 Analysis Populations

Study populations will be defined as follows:

- Safety and Efficacy Population: all subjects who receive at least 1 dose of CMP-001 and at least 1 recorded post-baseline assessment of objective response, assessed according to Cheson 2007 criteria.

- Pharmacodynamic Population: All subjects receiving any amount of study medication (placebo or active) and having any measurable IP-10 data.

9.4 Disposition

The number and percentage of subjects who enroll into the study (sign informed consent), who are dosed with CMP-001, and who discontinue, and the primary reason for discontinuation will be summarized by dose group.

Study completion information, including the reason for study withdrawal, if applicable, will be presented in a by-subject data listing.

9.5 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics (age, sex, race, body weight, height, and BMI) will be summarized for each dose group using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage of subjects for categorical variables) for the Safety Population.

Cancer History: At Screening, lymphoma and any other cancer type history will be obtained, and will include date of diagnosis, and prior and concomitant therapies. Lymphoma history (age at diagnosis, duration of disease, prior treatments, and location of tumors) will be summarized by dose group using descriptive statistics for the Safety Population, and listed by subject.

Medical and Surgical History: Medical and surgical history (excluding lymphoma history) will be listed by subject. Medical history will be coded using the most recent version of the MedDRA available at the time of study start.

9.6 Protocol Deviations

Protocol deviations (including but not limited to failure to meet study eligibility criteria, use of disallowed concomitant medications, and study drug overdoses) will be presented by subject in a by-subject data listing. Prior to database lock all deviations will be reviewed and classified as major or minor.

10.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

10.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

CMP-001 drug product is supplied as a 5 mg/ml concentration. CMP-001 is a colorless to pale yellow/brown opalescent liquid.

NOTE: CMP-001 may require a dilution at the investigational site to a 1.0 mg/mL using normal saline (refer to Pharmacy Manual for diluting instructions). **Table 5**

Pembrolizumab will be provided by Merck as summarized in Table 11.

Table 11 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4mL	Solution for Injection

10.2 Packaging and Labeling Information

Supplies will be labeled in accordance with regulatory requirements.

10.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the participant, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

10.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

10.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the participants and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

APPENDIX A. ECOG PERFORMANCE STATUS

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

APPENDIX B. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V4.0 (CTCAE) AND LEE 2014 CRS CRITERIA

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

Lee 2014 CRS grading criteria: (https://www.ncbi.nlm.nih.gov/pubmed/24876563)

Grade	Toxicity
Grade 1	Symptoms are not life threatening and require symptomatic treatment only, eg, fever, nausea, fatigue, headache, myalgias, malaise
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement <40% or Hypotension responsive to fluids or low dose[2] of one vasopressor or Grade 2 organ toxicity
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement ≥40% or Hypotension requiring high dose* or multiple vasopressors or Grade 3 organ toxicity or grade 4 transaminitis
Grade 4	Life-threatening symptoms Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
Grade 5	Death

APPENDIX C. CONTRACEPTIVE GUIDANCE AND PREGNANCY TESTING

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

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 no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in section 5.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 12 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 12 during the protocol-defined time frame in Section 5.1.

Table 12 Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b, c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b, c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● 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 treatment. 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.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 5 months after the last dose of study treatment. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test and in accordance with local requirements. Schedule as per Flow Chart 7.0

APPENDIX D. DESCRIPTION OF THE CHESON 2007 CRITERIA FOR ASSESSMENT OF DISEASE RESPONSE

Response criteria were adapted from Cheson 2007 and Lugano 2014.

CHESON 2007

Refer to Cheson 2007 publication for complete guide on the response criteria. (Cheson et al., 2007). Lugano classification may be consulted for any clarification especially for PET based response assessment.

Table 2. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

Table 3. Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

Table 3. Revised Criteria for Response Assessment (continued)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

APPENDIX E. DATA AND SAFETY MONITORING PLAN

Type of Clinical Trial:

- ☑ Investigator-initiated (UI/HCCC)
- ❑ Investigator-initiated, participating site
- ❑ Pilot study
- ❑ Phase I
- ☑ Phase I/II
- ❑ Phase II
- ❑ Phase III
- ❑ Compassionate-use/Expanded Access
- ☑ Interventional Treatment
- ❑ Interventional Non-Treatment
- ❑ Non-Interventional

Study risk-level:

- ❑ Level 1—low risk of morbidity or death, * <1% of death or any adverse event
- ❑ Level 2—risk of death* <1% or any adverse event 1% – 5%
- ❑ Level 3—risk of death* 1% – 5% or grade 4 – 5 SAE 1% – 5%
- ☑ Level 4—risk of death* >5% or grade 4 – 5 SAE >5%
- ❑ Drugs being used on a "compassionate" basis

***** *Risk of death" refers specifically to 100-day treatment-related mortality*

Reporting and Monitoring Requirements:

All institutional investigator initiated trials (IITs), regardless of assigned risk level are subject to routine DSMC monitoring activities which may include but are not limited to review of signed consent documents, eligibility and adverse event reporting.

All institutional IITs have the following **reporting requirements** as part of their DSMP:

- Register all subjects in HCCC's Clinical Trial Management System, OnCore
- Document Adverse Events
- Document protocol deviations
- Provide an annual progress report to the DSMC via OnCore data export

Selected monitoring strategy based on risk-level:

Risk Level 4

Interventional treatment trials involving investigational agents or devices with a risk of death* (>5% or grade 4 – 5 SAE >5%), e.g. all investigator initiated INDs, most Phase I/II trials, gene therapy, gene manipulation or viral vector systems high-risk clinical procedures if performed solely for research purposes. The use of a new chemical or drug for which there is limited or no available safety data in humans.

Study Safety Review

An independent study monitor and/or the DSMC Chair (or designee), will review study data (provided by the PI/available in OnCore) and communicate with the PI at least biannually. A copy of this communication will be forwarded to the DSMC and PRMC Chairs.

Additional Reporting Requirements:

- A scanned copy of the completed eligibility checklist, with screening information and PI signature, will be attached in OnCore for ongoing review by DSMC staff.
- Serious adverse events will be entered directly into an OnCore SAE report by the research team. OnCore will send an automatic notification to the DSMC Chair/acting Chair and staff for review.
- The DSMC utilizes a risk-based monitoring approach. The trial's research records will be monitored at minimum twice per year. Monitoring may be done more frequently depending on the protocol, risks to subjects, reported serious/adverse events, patient population and accrual rate. Records for a minimum of 25% of subjects will be monitored for the entire study.

  Monitoring will involve the following:

  - review eligibility of patients accrued to the study,
  - check for the presence of a signed informed consent,
  - determine compliance with protocol's study plan,
  - determine whether SAEs are being appropriately reported to internal and external regulatory agencies,
  - compare accuracy of data in the research record with the primary source documents,
  - review investigational drug processing and documentation,
  - assess cumulative AE/SAE reports for trends and compare to study stopping rules.

Routine Adverse Event Reporting

For non-serious Adverse Events, documentation must begin after the subject signs the Informed Consent Document until 30 days after the last dose of CMP-001. Collected information should be recorded in the electronic/Case Report Forms (eCRF/CRF) for that subject. A description of the event, its severity or toxicity grade (according to NCI's Common Toxicity Criteria (CTCAE)),

onset and resolved dates (if applicable), and the relationship to the study drug should be included. Documentation should occur in real time. The principal investigator has final responsibility for determining the attribution of the event as it is related to the study drug.

Serious Adverse Event Reporting

For any experience or condition that meets the definition of a serious adverse event (SAE), recording of the event must begin after signing of the informed consent and continue through the 30 days after the last dose of CMP-001.
Investigators must report to the DSMC any serious adverse events (SAE), whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64). SAEs must be reported via an OnCore SAE Report within 24 hours of learning of the event.

An adverse event is considered **serious** if it results in ANY of the following outcomes:

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization OR prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.
6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

FDA Reporting Requirements (for Sponsor-Investigators)

It is the responsibility of the IND sponsor-investigator to comply with IND safety reporting as set forth in the Code of Federal Regulations, Section 312.32. This responsibility includes providing an annual IND report to the FDA.

All IND safety reports must be submitted on Form 3500A and be accompanied by Form 1571. The type of report (initial or follow-up) should be checked in the respective boxes on Forms 3500A and 1571. See Instructions for completing Form 3500A. Please note all instance of UIHC, location, and faculty / staff should be redacted from supporting documentation and the 3500A.

Instructions for completing Form 3500A. Please note all instance of UIHC, location, and faculty / staff should be redacted from supporting documentation and the 3500A.

The submission must be identified as:

- "IND safety report" for 15-day reports, or

- "7-day IND safety report" for unexpected fatal or life-threatening suspected adverse reaction reports, or
- "Follow-up IND safety report" for follow-up information.

For detailed explanation of the above definitions, requirements, and procedures related to IND application safety reports and the responsibilities of IND applications sponsors with regard to such reporting, refer to Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies (PDF - 227KB)

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome, if known (grading the event per CTCAE)
- Supportive laboratory results and diagnostics
- Sponsor-Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Data Monitoring and Management

Subject Registration

All studies that undergo PRMC review and/or utilize HCCC Clinical Research Services (CRS) resources are required to register subjects in OnCore. Each subject registration includes the following:

- The subject's IRB approved (version date) consent form and the date of their consent.
- Date of eligibility and eligibility status (eligible, not eligible)
- On study date and subject's disease site (and histology if applicable)
- On treatment date (if applicable)

All subject registration information is expected to be entered into OnCore within **2 (two) business days** after the subject's study visit.

Subject Data

For HCCC investigator initiated trials, research staff are responsible for entering subject study data (data collection) into OnCore electronic case report forms (eCRFs). These eCRFs must be approved by the PI and statistician prior to study activation to ensure sufficient and necessary data acquisition. All information entered into eCRFs will be traceable to the source documents which are generally maintained in the subject's file.

eCRF data entry needs to be timely and should be entered into OnCore as soon as possible but no later than **14 (fourteen) business days** after the subject's visit, including adverse events, tumor measurements, administration of study medication, concomitant medications, labs, and vitals. Physical exam assessments must be entered no later than **14 (fourteen) business days** following completion of the physician's clinic note in the medical record.

Timely data entry facilitates remote monitoring of data, allows the data to progress appropriately through the data cleaning process, and helps prevent a backlog of data queries.

Forms Monitoring

OnCore eCRF data are monitored on a routine basis (dependent on accrual) to ensure all data are entered completely, accurately, and within time requirements outlined above. The assigned DSMC monitor will coordinate and complete the data monitoring review. When the time comes to monitor a study (based on patient accrual and assigned risk level of trial) the monitor arranges for a selection of cases to be reviewed from among the subjects registered in OnCore. As part of the forms monitoring process, the assigned monitor will issue queries via OnCore (linked to the eCRF) to resolve missing, incomplete, and/or incorrect information. A member of the research team is expected to respond to these monitoring queries within **14 (fourteen) business days.**

The monitoring process can often identify misunderstandings or deficiencies in the written, research protocol requirements earlier in the study process and thereby improve data quality and reduce rework.

Final Reports

A summary of each subject's data record is continually available to the PI, research staff, and DSMC from OnCore's Biostat Console. The availability of this information is a valuable tool for the preparation of final reports and manuscripts as well as ongoing deficiency reports.

APPENDIX F. BOIN12 TRIAL DESIGN CHARACTERISTICS

Table A. Rank-based desirability score (RDS) table for the BOIN12 design, where "E" means elimination. A larger value of RDS means higher desirability, and any value of RDS is deemed higher than "E". **#Pts** denotes the number of evaluable patients treated at current dose; **#Tox** denotes the number of evaluable patients who experience toxicity; **#Eff** denotes the number of evaluable patients who experience efficacy.

#Pts	#Tox	#Eff	RDS	#Pts	#Tox	#Eff	RDS	#Pts	#Tox	#Eff	RDS	#Pts	#Tox	#Eff	RDS
0	0	0	62	**6**	3	5	74	**9**	4	3	4	**12**	2	11	106
3	0	<= 0	E	**6**	3	6	93	**9**	4	4	15	**12**	2	12	116
3	0	1	42	**6**	>= 4	Any	E	**9**	4	5	33	**12**	3	<= 3	E
3	0	2	69	**9**	0	<= 2	E	**9**	4	6	48	**12**	3	4	3
3	0	3	96	**9**	0	3	19	**9**	4	7	67	**12**	3	5	12
3	1	<= 0	E	**9**	0	4	36	**9**	4	8	84	**12**	3	6	26
3	1	1	34	**9**	0	5	54	**9**	4	9	102	**12**	3	7	41
3	1	2	60	**9**	0	6	72	**9**	>= 5	Any	E	**12**	3	8	57
3	1	3	88	**9**	0	7	89	**12**	0	<= 3	E	**12**	3	9	73
3	2	<= 0	E	**9**	0	8	104	**12**	0	4	11	**12**	3	10	87
3	2	1	27	**9**	0	9	117	**12**	0	5	24	**12**	3	11	103
3	2	2	53	**9**	1	<= 2	E	**12**	0	6	40	**12**	3	12	114
3	2	3	80	**9**	1	3	14	**12**	0	7	56	**12**	4	<= 3	E
3	>= 3	Any	E	**9**	1	4	30	**12**	0	8	71	**12**	4	4	2
6	0	<= 1	E	**9**	1	5	47	**12**	0	9	86	**12**	4	5	9
6	0	2	28	**9**	1	6	65	**12**	0	10	101	**12**	4	6	22
6	0	3	49	**9**	1	7	82	**12**	0	11	113	**12**	4	7	37
6	0	4	70	**9**	1	8	100	**12**	0	12	119	**12**	4	8	52
6	0	5	91	**9**	1	9	115	**12**	1	<= 3	E	**12**	4	9	68
6	0	6	110	**9**	2	<= 2	E	**12**	1	4	8	**12**	4	10	83
6	1	<= 1	E	**9**	2	3	10	**12**	1	5	20	**12**	4	11	98
6	1	2	23	**9**	2	4	25	**12**	1	6	35	**12**	4	12	112
6	1	3	44	**9**	2	5	43	**12**	1	7	50	**12**	5	<= 3	E
6	1	4	64	**9**	2	6	59	**12**	1	8	66	**12**	5	4	1
6	1	5	85	**9**	2	7	77	**12**	1	9	81	**12**	5	5	6
6	1	6	105	**9**	2	8	95	**12**	1	10	97	**12**	5	6	17
6	2	<= 1	E	**9**	2	9	111	**12**	1	11	109	**12**	5	7	32
6	2	2	18	**9**	3	<= 2	E	**12**	1	12	118	**12**	5	8	46
6	2	3	39	**9**	3	3	7	**12**	2	<= 3	E	**12**	5	9	63
6	2	4	58	**9**	3	4	21	**12**	2	4	5	**12**	5	10	78
6	2	5	79	**9**	3	5	38	**12**	2	5	16	**12**	5	11	94
6	2	6	99	**9**	3	6	55	**12**	2	6	29	**12**	5	12	108
6	3	<= 1	E	**9**	3	7	75	**12**	2	7	45	**12**	>= 6	Any	E
6	3	2	13	**9**	3	8	90	**12**	2	8	61				
6	3	3	31	**9**	3	9	107	**12**	2	9	76				
6	3	4	51	**9**	4	<= 2	E	**12**	2	10	92				

Table B. Operating characteristics of the BOIN12 design.

	CMP-001 Dose Level		
	7.5 mg	**10 mg**	**Stop %**
Scenario 1			
DLT rate	0.2	0.2	
Efficacy rate	0.1	0.1	
No. Pts treated	4.2	3.7	
Select %	1.9	1.2	96.9
Scenario 2			
DLT rate	0.2	0.2	
Efficacy rate	0.1	0.2	
No. Pts treated	4.2	5.2	
Select %	2.3	10.7	87
Scenario 3			
DLT rate	0.2	0.2	
Efficacy rate	0.2	0.3	
No. Pts treated	5.7	6.5	
Select %	12.4	26.1	61.5
Scenario 4			
DLT rate	0.2	0.2	
Efficacy rate	0.3	0.4	
No. Pts treated	6.8	7.5	
Select %	26.3	40.3	33.4
Scenario 5			
DLT rate	0.2	0.2	
Efficacy rate	0.4	0.5	
No. Pts treated	7.6	8	
Select %	35.8	48.8	15.4
Scenario 6			
DLT rate	0.2	0.2	
Efficacy rate	0.5	0.5	
No. Pts treated	8.7	7.2	
Select %	52.3	38.2	9.5
Scenario 7			
DLT rate	0.3	0.3	
Efficacy rate	0.4	0.5	
No. Pts treated	7.8	6.4	
Select %	40.3	29.5	30.1
Scenario 8			
DLT rate	0.3	0.3	
Efficacy rate	0.5	0.5	
No. Pts treated	8.9	5.7	

	CMP-001 Dose Level		
	7.5 mg	**10 mg**	**Stop %**
Select %	53.9	22.9	23.2
Scenario 9			
DLT rate	0.4	0.4	
Efficacy rate	0.4	0.5	
No. Pts treated	7.7	4.4	
Select %	35.3	11.9	52.7
Scenario 10			
DLT rate	0.4	0.4	
Efficacy rate	0.5	0.5	
No. Pts treated	8.6	3.9	
Select %	44.8	9.1	46.1
Scenario 11			
DLT rate	0.5	0.5	
Efficacy rate	0.4	0.5	
No. Pts treated	7.1	2.7	
Select %	21.3	3	75.6
Scenario 12			
DLT rate	0.5	0.5	
Efficacy rate	0.5	0.5	
No. Pts treated	7.8	2.5	
Select %	26.8	2.5	70.7

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