USC Norris Comprehensive Cancer Center
Part of the Keck School of Medicine of USC

Local Protocol #: 0C-19-19

Protocol Title: The Seena Magowitz Phase IB/II Trial of CMP-001 (a TLR9 agonist) in Combination with INCAGN01949 (an activating anti-OX40 antibody) for In Situ Intratumoral Injection for Patients with Stage IV Pancreatic and other Cancers except Melanoma
Protocol version date: 03/12/2021

ClinicalTrialsgov #: NCT04387071

The Seena Magowitz Phase IB/II Trial of CMP-001 (a TLR9 agonist) in Combination with INCAGN01949 (an activating anti-OX40 antibody) for In Situ Intratumoral Injection for Patients with Stage IV Pancreatic and other Cancers except Melanoma

IND 19516

SPONSOR:

UNIVERSITY OF SOUTHERN CALIFORNIA (USC)

STUDY SITES:

HONORHEALTH, SCOTTSDALE, AZ

USC Norris Comprehensive Cancer Center, Los Angeles, CA

Hoag Memorial Hospital Presbyterian, Newport Beach, CA

Stanford University, Stanford, CA

Protocol No. 0C-19-19/TGen 19-001

March 12, 2021

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This study is funded and administered by the research teams at:

Funding Provided By: Seena Magowitz Foundation

CONFIDENTIAL

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Study Drug: CMP001, INCAGN01949

IND Number: 19516

IND Holder Name: University of Southern California

Funding Source: **Seena Magowitz Foundation**

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INVESTIGATOR PROTOCOL AGREEMENT

Protocol#:	0C-19-19/TGen 19-001
Protocol Title:	The Seena Magowitz Phase IB/II Trial of CMP-001 (a TLR9 agonist) in Combination with INCAGN01949 (an activating anti-OX40 antibody) for In Situ Intratumoral Injection for Patients with Stage IV Pancreatic and other Cancers except Melanoma
Protocol Version/Date:	March 12, 2021

I confirm that my staff and I have carefully read and understand this protocol. I/we agree to comply with the procedures and terms of the clinical trial specified herein. In particular, I/we have agreed to:

- Abide by all obligations as required by local and federal regulatory authorities.
- Comply with Good Clinical Practice (GCP) and all applicable regulatory requirements.
- Maintain confidentiality and assure security of Sponsor and confidential documents
- Obtain Institutional Review Board (IRB) approval of the protocol, any amendment to the protocol, and periodic re-approval as required, and to keep the IRB informed of any adverse events and periodically report the status of the trial to them.
- Not implement any deviations from or changes to the protocol without agreement from the sponsor and prior review and written approval from the IRB, except where necessary to eliminate an immediate hazard to the patients or for administrative aspects of the trial (where permitted by all applicable regulatory requirements).
- Assure that each patient enrolled into the trial has read, understands, and has signed the informed consent.
- Ensure that I and all persons assisting me with the trial are adequately informed and trained about the investigational drug and of their trial-related duties and functions as described in the protocol.
- Make prompt reports of serious adverse events (SAEs) and deaths (within 1 business day of learning of the death and/or of learning of the SAE) to Sponsor.
- Assure access by Sponsor including assigned CRO and/or FDA to original source documents.
- Prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated in the investigation.
- Arrange for the transfer of appropriate data from case histories to case report forms for the collection and transmission of data to the Sponsor.
- Retain records and documents related to this trial for at least 3 years after the completion of the trial as confirmed by the sponsor.
- Cooperate fully with any trial-related GCP audit as performed by the assurance group specified by the Sponsor.
- Abide by the stipulations in the Disclosure of Data section and the manuscript preparation/authorship guidelines established at the outset of the trial.

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Investigator's Printed Name: _____

Institutional Name: _____

Investigator' Signature: _____ Date: _____

Glossary of Abbreviations	
Term	**Definition**
ADA	Antidrug antibody
ADL	Activity of Daily Living
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	Anti-nuclear antibody
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BPI	Brief Pain Index
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CA-125	Cancer Antigen 125
CA 19-9	Carbohydrate Antigen 19-9
CBC	Complete Blood Count
CEA	Carcinoembryonic Antigen
CFR	Code of Federal Regulations
CIC	Clinical investigations committee
CISO	Clinical investigations support office
CNS	Central Nervous System
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CRS	Cytokine release syndrome
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DHHS	Department of Health and Human Services
DLT	Dose Limiting Toxicity
DSMC	Data Safety and Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End of Treatment
ERC	Ethics Review Committee
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference of Harmonisation

Glossary of Abbreviations	
Term	**Definition**
IDO	Indoleamine 2,3- dioxygenase
IFNα	Interferon alpha
INR	International Normalized Ratio
IO	Immuno-oncology
irAE	Immune-related Adverse Event
IRB	Institutional Review Board
iRECIST	Immunotherapy Response Evaluation Criteria in Solid Tumours
IT	Intra-tumor
IUD	Intrauterine Device
IV	Intravenous
LDH	Lactate Dehydrogenase
mAb	Monoclonal Antibody
MTD	Maximum Tolerated Dose
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
NCCC	Noriss comprehensive cancer center
NCI	National Cancer Institute
NIH	National Institutes for Health
NS	Normal saline
ODN	Oligodeoxynucleotide
OS	Overall Survival
OTC	Over-the-counter
PD	Progressive Disease
PDAC	Pancreatic Ductal Adenocarcinoma
pDC	Plasmacytoid dendritic cell
PFS	Progression Free Survival
PR	Partial Response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QbG10	Qb packaged with the oligonucleotide G10 (referred to as the active drug substance)
RECIST	Response Evaluation Criteria in Solid Tumors
ROA	Route of administration
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Stable Disease
SOP	Standard Operating Procedure
SubQ	Subcutaneous
TGen	Translation Genomic Research Institute
TLR9	Toll-like receptor 9
ULN	Upper Limit of Normal

Glossary of Abbreviations	
Term	**Definition**
VLP	Virus-like particle
WOCBP	Woman Of Childbearing Potential

TRIAL SCHEMATIC

The study is divided into two phases:

Phase IB
N = 3-21 patients

Patients with previously treated (for their metastatic disease) pancreatic ductal adenocarcinoma and other types of cancer, except melanoma, will be enrolled (1-3 pts each dose level) in up to 6 dose cohorts of a fixed dose of CMP-001 (TLR9 agonist) + INCAGN01949 (OX40 agonist).

Note: Dosing schedule is done on a weekly basis. Week 1 day 1 is the first dose of CMP-001 given SC. The first two weeks of treatment (dose 1 and 2) are only with CMP-001 administered subcutaneously (SC) at a dose of 5mg. After this priming period with CMP-001 both investigational agents (CMP-001 and INCAGN01949) will be given via intratumor (IT) administration. The remaining 4 weeks (doses 3-6) of the study both agents will be given IT (CMP-001 will be given at 10mg during IT administration). Biopsies will be done before the first SC treatment, before the 2nd IT treatment and before the 4th IT treatment (e.g. before week 1, before week 4 and week 6).

Endpoint for this phase IB portion of the study is determining the doses and tolerance, effect on biomarkers and recommended

MTD Phase II Dose

Phase II
N = 10-21 patients

Determine the efficacy (Disease Control Rate defined as CR+ PR+ SD X 16 weeks) of Phase I (MTD) selected dose of CMP-001 (TLR9 agonist) in combination with INCAGN01949 (anti-OX40 antibody) for patients with previously treated (for their metastatic disease) pancreatic ductal adenocarcinoma

	CMP-001	**INCAGN01949**
Wk1	5mg SC	No dose, CMP-001 SC only
Wk2	5mg SC	No dose, CMP-001 SC only
Wk3	10mg IT	Dose level 1, 2, 3, 4, 5, 6
Wk4	10mg IT	Dose level 1, 2, 3, 4, 5, 6
Wk5	10mg IT	Dose level 1, 2, 3, 4, 5, 6
Wk6	10mg IT	Dose level 1, 2, 3, 4, 5, 6

TRIAL SYNOPSIS

Protocol#:	0C-19-19/TGen 19-001
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Short Title:	Intratumoral TLR9 agonist plus OX40 Agonist in PDAC and other Cancers (except melanoma)
Protocol Version/Date:	March 12, 2021
Sponsor:	University of Southern California (USC)
Trial Sites:	HonorHealth, Scottsdale, AZ USC Norris Comprehensive Cancer Center, Los Angeles, CA Hoag Memorial Hospital, Newport Beach, CA Stanford University, Stanford, CA
Lead Principal Investigators:	Diana Hanna, MD
Clinical Phase:	Phase IB/II
Trial Design:	Phase IB/II Pilot Trial
Objectives:	
Primary:	• Phase IB: To determine the maximum tolerated dose and tolerance of CMP-001 (TLR9 agonist) in combination with INCAGN01949 (an activating antibody against OX40) both given intratumorally for patients with previously treated (for their metastatic disease) pancreatic ductal adenocarcinoma and other types of cancer except melanoma. • Phase II: To determine the efficacy (Disease control rate - CR + PR + SD X 16 weeks) of CMP-001 (TLR9 agonist) in combination with INCAGN01949 (OX40 agonist antibody) for patients with previously treated (for their metastatic disease) pancreatic ductal adenocarcinoma. • To determine effects on tumor markers.
Secondary:	• Define the toxicity of the combination of CMP-001 (TLR9 agonist) + INCAGN01949 (OX40 agonist antibody) • Determine progression free survival and overall survival
Exploratory:	• Using flow cytometry on peripheral blood, OX40 expression will be analyzed within the lymphocyte subsets (Teffs and Tregs). • On tissue samples collected prior to, and during treatment, we will:

	– Use flow cytometry to enumerate CD4+ and CD8+ T cell subsets, and the expression of activation/differentiation markers (including CD127, HLA-DR, CD45RO, CCR7, CXCR3) on each – Use RT-PCR and sequencing to amplify and characterize the TCRa and b sequences of tumor-infiltrating T cells, looking for evidence of oligo-clonal T cell expansion, OX40 expression - If there is adequate tumor tissue, perform RNAseq to determine different immune cell populations, including T cells and macrophages
Endpoints:	
Primary:	• Phase IB: Doses and tolerance and recommended Phase II dose • Phase II: Disease control rate (CR+PR+SD x 16 weeks via RECIST and iRECIST) and effects on tumor markers
Secondary:	• Incidence of toxicities • Progression free survival and overall survival
Exploratory:	• To determine OX40 expression within the lymphocyte subsets (Teff and Treg) • On tissue samples collected prior to, and during, treatment, we will: – Use flow cytometry to enumerate CD4+ and CD8+ T cell subsets, tumor cells, and the expression of activation/differentiation markers (including CD127, HLA-DR, CD45RO, CCR7, CXCR3) on each – Use RT-PCR and sequencing to amplify and characterize the TCRa and b sequences of tumor-infiltrating T cells, looking for evidence of oligo-clonal T cell expansion, OX40 expression - If there is adequate tumor tissue, perform RNAseq to determine different immune cell populations, including T cells and macrophages
Statistical Methods:	The sample size of this pilot study will be up to 21 patients in Phase IB. In phase II, we will treat an initial cohort of 10 patients, and if there

	are no patients with disease control defined as (CR+PR+stable disease x 16 weeks) the trial will be closed. If there are 1 or more patients with disease control, the trial will be expanded to 21 patients with pancreatic cancer. Four or more patients with disease control out of 21 patients will be sufficient evidence for rejection of the null hypothesis of insufficient activity of the regimen. This design has a power of 90% at a one-sided Type I error rate of 2.5%.
Statistical Methods for Efficacy:	The efficacy analysis will include summaries for the following parameters: complete response rate (CR), objective response rate (CR + PR), disease control rate (CR + PR + SD at 16 weeks), percent of patients who have decrease in tumor marker, progression-free survival (PFS), and overall survival (OS). The efficacy analysis will only be conducted on patients who have received at least one dose of CMP-001 and of INCAGN01949 and have at least one post baseline tumor assessment. Objective responses will be evaluated using the Response Evaluation Criteria In Solid Tumors 1.1 (RECIST 1.1) and iRECIST. Changes (i.e. improvements) in tumor measurements from baseline values will be assigned a status of CR or PR or SD. Objective response measurements will comprise the sum of CR plus PR. The overall response rate, as well as the rates for the individual categories of response (i.e. CR, PR, SD, and PD) will be estimated by the percentage of patients who have received at least one dose of CMP-001 and of INCAGN01949 achieving these criteria. The disease control rate will consist of the sum of CR + PR + SD for 16 weeks. All proportions will be estimated using an exact 95% binomial confidence interval. For the estimation of progression-free and overall survival, a Kaplan-Meier analysis will be performed. Tumor assessments for evaluation of response will be conducted using CT or MRI, approximately every 8 weeks until study discontinuation or disease progression, whichever is later. All sites of disease must be followed using the same baseline assessment method. Confirmatory assessment of complete response (CR) or partial response (PR) must be performed no less than 4 weeks after the initial documentation of response. All target lesions will be measured by consistent imaging techniques for each patient throughout the study. Suitable imaging techniques include CT-scan, or MRI. The same technique should be used for each evaluation in an individual patient. Copies of the scans must be available for review. Progression-free survival is defined as the interval from the date of registration (i.e. assignment of patient number) to the earliest date of documented evidence of recurrent or progressive disease, or the date of death due to any cause, whichever occurs first. Patients who do not progress and remain alive will be censored at their last radiographic assessment date. Overall survival will be measured from the date of registration (i.e. assignment of patient number) to

<table>
<tr><td></td><td>the date of death due to any cause, or the date of last contact (censored observations).</td></tr>
<tr><td>Statistics for Safety:</td><td>All patients who receive any dose of CMP-001 or INCAGN01949 will be included in the following safety analyses:

• The incidence, severity, duration, causality, seriousness, and type of AEs

• Changes in the patient's physical examination, vital signs, and clinical laboratory results

• Grading of clinical laboratory results per CTCAE version 5.0 criteria for selected laboratory parameters

• Deaths

• Concomitant medications</td></tr>
<tr><td>Name, dose of investigational agents:</td><td>The first two doses of CMP-001 are given subQ at a dose of 5mg while the remaining doses are given intratumorally (IT) at 10mg. All doses of INCAGN01949 are given IT

<u>CAUTION</u>:
INCAGN01949 is in micrograms per meter squared

<table>
<tr><th>Dose Level</th><th>CMP-001 (mg)</th><th>INCAGN01949 (mcg/m^2)</th></tr>
<tr><td>-1</td><td>5 (IT)</td><td>250 (IT)</td></tr>
<tr><td>1</td><td>10 (IT)</td><td>500** (IT)</td></tr>
<tr><td>2</td><td>10 (IT)</td><td>1000 (IT)</td></tr>
<tr><td>3</td><td>10 (IT)</td><td>1670 (IT)</td></tr>
<tr><td>4</td><td>10 (IT)</td><td>2505 (IT)</td></tr>
<tr><td>5</td><td>10 (IT)</td><td>3507 (IT)</td></tr>
<tr><td>6</td><td>10 (IT)</td><td>4559* (IT)</td></tr>
</table>
* If higher dose levels are needed, escalation will be in 50% increments
** The 500mcg/m2 dose of INCAGN01949 will be reconstituted to a volume of 1ml INCAGN01949 will be supplied as 5 mL of aqueous solution in 10 mL glass vials with 10 mg/mL.

• Note: One patient per dose level until grade greater than or equal to grade 2 toxicity. Then 3 patients per level. Our recommended dose will be determined by induction of expression of OX40 on the CD4+ T cells.

• The dose escalation scheme used is a conservative modified Fibonacci method

• As currently designed, the first two CMP-001 doses will be given subcutaneously, and the following doses 3-6 will be</td></tr>
</table>

	given intratumorally (IT). All 4 doses of INCAGN01949 will be given IT. If the patient is judged to be having clinical benefit the possibility of being treated with additional doses will have to be dealt with via an amendment to this protocol. • The starting dose for intratumoral injection of INCAGN01949 is based on the known safety profile of intravenous INCAGN01949 at doses ranging from 7-1400 mg. The proposed starting dose is less than 10% of the intravenous route of administration and provides an additional margin for safety in the trial. There is the potential for OX40 upregulation following TLR9 agonist administration and its binding could produce cytokine release.
Total # of Patients:	Total of up to 21 in the Phase IB portion and up to 21 in the Phase II portion
Treatment Arms:	Arm 1: CMP-001 (TLR9 agonist) + INCAGN01949 (OX40 agonist antibody)
Patient Population:	Patients previously treated with stage IV pancreatic cancer and other appropriate types of metastatic cancers except melanoma.
Inclusion criteria:	1. Be willing and able to provide written informed consent for the trial. 2. Be ≥ 18 years of age. 3. Histologically or cytologically confirmed pancreatic adenocarcinoma with metastasis or other locally advanced un-resectable solid tumor malignancies (during the phase Ib and pancreatic cancer during phase II) deemed appropriate by the Investigator except melanoma. 4. Have a performance status of 0 or 1 on the ECOG performance scale. 5. Subjects must have at least one extra-central nervous system (CNS), non-bone tumor lesion amenable for IT injection ≥ 1.5 cm and that is not in close proximity or encasing crucial structures such as major blood vessels, trachea, nerve bundles etc. Measurable disease is required in a minimum of two lesions (one injected and one other) and there must be at least one measurable lesion in addition to the one being injected. 6. Be willing to undergo a needle biopsy of a tumor lesion at baseline, after 2 weeks of IT injection and 4 weeks of IT injection (Week 4 and 6), unless tumor is considered inaccessible or biopsy is otherwise considered not in the patients best interest. 7. Demonstrate adequate organ function as defined in Table 2.

	8. Female participants of childbearing potential should have a negative serum pregnancy test within 24 hours prior to receiving first dose of trial medication. 9. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies: a.) Not a woman of childbearing potential (WOCBP) OR b.) A WOCBP who agrees to follow the contraceptive guidance during the treatment period and for at least 180 days after the last dose of trial treatment. 10. Male participants must agree to use contraception as detailed in the full protocol during the treatment period and for at least 120 days after the last dose of trial treatment and refrain from donating sperm during this period. 11. Patients will have had at least 2 prior therapies for locally advanced, un-resectable and/or metastatic disease. Adjuvant therapy will count as one line of therapy if disease progression occurred during treatment or within 6 months of completion. Patients with metastatic pancreatic cancer must have received either FOLFIRINOX or a gemcitabine-based regimen as one of their prior lines of therapy. Patients with germline BRCA mutations must have received olaparib as maintenance therapy.
Exclusion criteria:	1. Is currently participating and receiving trial therapy or has participated in a trial of an investigational agent and received trial therapy or used an investigational device within 3 weeks (or 5 half-lives, whichever is shorter) of the first dose of trial treatment. 2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids (not to exceed a daily equivalent of Prednisone 10mg daily) may be approved after consultation with the Sponsor. If patients received prior ipilimumab or anti-CTLA4 compound and had adrenal insufficiency, treat these subjects with stress dose steroids prior to intratumoral injections. If patients are receiving stress steroids orally but if not able to have orally then they would be given IV before the procedure.

	3. Hypersensitivity to CMP-001 (TLR9 agonist) or INCAGN01949 (OX40 agonist antibody) or any of its excipients. 4. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to Week 1/Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier. 5. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 3 weeks prior to Week1/ Day 1 or who has not recovered (i.e., ≤ Grade 1 or to baseline) from adverse events due to a previously administered agent(s). **Note**: Patients with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the trial. **Note**: If patient received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy. 6. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer. Other malignancies which have been treated with curative intent, or for which patients are not receiving active therapy, may be considered upon discussion with the Investigator. 7. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. Use of prophylactic anti-epileptic drugs is permitted. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability. 8. 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 (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. 9. Has history of (non-infectious) pneumonitis that required steroids or currently has pneumonitis.

	10. Has an active infection requiring systemic therapy. 11. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator. 12. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. 13. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies). 14. Has a known history of or is positive for Hepatitis B (e.g., HBsAg reactive) or untreated Hepatitis C. Treated Hepatitis C with sustained virologic response and patients who are negative for Hepatitis BsAg are not excluded. **Note:** Without known history, testing needs to be performed to determine eligibility. 15. Current, serious, clinically significant cardiac arrhythmias as determined by the treating investigator. 16. Has received a live vaccine within 30 days of planned start of trial therapy. **Note**: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed. 17. Patients must not be receiving any anticoagulation. Low molecular weight heparin at full dose or prophylactic dose is allowed as long as the treating physician deems it safe to hold the LMWH on the day before and the day of the intra-tumoral injection.

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TABLES

1.0 BACKGROUND AND RATIONALE

Overview

Pancreatic cancer continues to be a very lethal disease. It is estimated that in 2019, 56,770 Americans will be diagnosed with pancreatic ductal adenocarcinoma (PDAC), and 45,750 will die from the disease. This makes pancreatic cancer the third leading cause of death from cancer in the US (Siegel et al 2019). Furthermore, it is projected that by 2030, PDAC will be the second leading cause of death from cancer in the US. Worldwide, PDAC is the twelfth most common cancer, accounting for an estimate of > 300,000 deaths a year (Rahib et al 2014).

Detection of pancreatic cancer has been notoriously very late in the disease and therefore the 5-year survival rate is only 8%. Right now, the only potential cure for pancreatic cancer is surgical resection (if the disease is caught early). However, only about 20% of PDAC patients are eligible for potentially curable resection and unfortunately most (> 80%) have reoccurrence of their cancer within 2 years of resection, and those reoccurrences are almost universally fatal (Oettle et al 2013 and Neoptolemos et al 2010). Improved strategies for early detection and for treatment of PDAC are desperately needed.

Immunotherapy has become an effective treatment for many cancer types with cures in previously untreatable cancers (Ascierto et al 2017). However, these immunotherapies have largely proven unsuccessful in pancreatic cancer. One of the reasons for this may be due to an unfavorable microenvironment that makes pancreas tumors immunologically "cold" (non-responsive) (Skelton et al 2017).

Rationale for the use of TLR9 + OX40

A promising new area of immunotherapy involves activating both the innate and the adaptive immune systems. This approach is called in-situ vaccination where immunoenhancing agents are injected into the tumor, which triggers a T cell response throughout the body (attacking local and metastatic tumors). The combination proposed here uses a TLR9 agonist (CMP-001) and an OX40 agonist (INCAGN01949). This technique is particularly interesting because it doesn't require prior knowledge of the unique tumor antigens in the patient (Sagiv-Barfi et al 2018).

The paper by Sagiv-Barfi et. al. showed how in situ vaccination could cure several different mouse models of cancer via a single course (intratumor injection on days 1, 3, and 5) of two immune-enhancing agents (Fig 1). The first agent is CpG, a Toll-like receptor 9 (TLR9) agonist known as CMP-001 followed by an anti-OX40 antibody (INCAGN01949) that acts as an agonist triggering a T cell immune response. This approach not only cured tumors that were injected with both agents but also distant tumors that were not injected. This combination also led to cures in a spontaneous mouse tumor model. We believe the intratumor injection and immunoenhancing properties of the approach will result in responses not previously seen using IO agents

in pancreatic and other cancers. In addition, local injections can likely avoid systemic side effects experienced by intravenously administered IO agents.

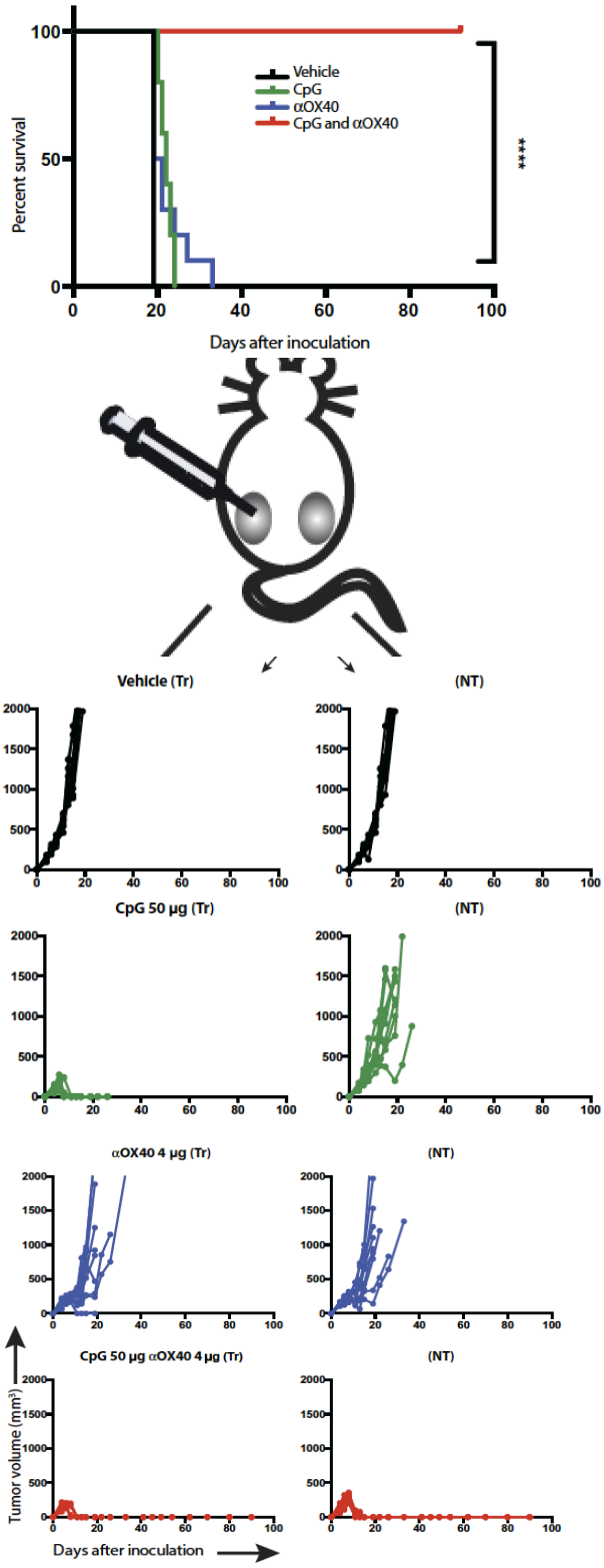


Fig. 1. Tumor growth curves. Left column: Treated tumors (Tr). Right column: Nontreated tumors (NT). Top to bottom: Vehicle, CpG, aOX40, and CpG and aOX40 and survival plots of the treated mice (n = 10 mice per group). ****P <0.0001, unpaired t test. Shown is one representative experiment out of nine. (C) Effect of CD4/CD8 depletion. Mice were implanted with bilateral tumors, and one tumor was injected with CpG and aOX40 antibody according to the schema in (A). CD4 (0.5 mg)–and CD8 (0.1 mg)–depleting antibodies were injected intraperitoneally on days 6, 8, 12, and 15 (n = 10 mice per group). (D) CD8 T cell immune response. Splenocytes from the indicated groups obtained on day 7 after treatment were cocultured with media, 1 × 10^6 irradiated 4T1 cells (unrelated control tumor), or A20 cells (homologous tumor) for 24 hours. Intracellular IFN-g was measured in CD8+ T cells by flow cytometry as a percentage of CD44hi (memory CD8) T cells shown in dot plots and bar graph, summarizing data from three experiments (n = 9 mice per group). ****P < 0.0001, unpaired t test

Sagiv-Barfi et al Sci. Transl. Med. 2018

CMP-001 Background

CMP-001 is an immunostimulatory therapeutic agent that may have anti-tumor activity for a variety of different types of cancer. The initial Phase 1b study CMP-001-001, *A Multicenter, Open-Label, Phase 1b Clinical Study of CMP-001 in Combination with Pembrolizumab in Subjects with Advanced Melanoma* (NCT02680184) has completed enrollment (Milhelm et al., SITC, 2020).

CMP-001 is composed of (i) a virus-like particle (VLP) comprised of capsid proteins derived from bacteriophage Qbeta, which encapsulate (ii) a CpG-A 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 (pDCs). The therapeutic agent is a VLP referred to as QbG10.

QbG10 has been previously studied in clinical trials under the name CYT003. In the Investigator's Brochure, the name CYT003 referred to historical data using the investigational drug product in non-oncology settings. In this present study the name CMP-001 will refer to the Checkmate Pharmaceuticals' (Checkmate) investigational drug product. CYT003 was renamed CMP-001 when Checkmate took over development in oncology settings, but the two are the same drug.

Administration of CMP-001 is intended to activate TLR9 in pDC within the tumor or the tumor-draining lymph nodes (tumor-associated pDC). 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 via IT administration, or in the draining lymph nodes via SC administration. CMP-001 has been tested at doses of 1mg, 3mg, 5mg, 7.5mg, 10 mg, 12.5 mg, 15 mg and 17.5 mg in clinical trials either as monotherapy or in combination with Pembrolizumab (Milhelm et al., SITC, 2020), Atezolizumab (Negrao et al., WCLC, 2021) or Nivolumab (Davar et al., SITC, 2020).

CMP-001 is currently being evaluated in 3 ongoing Checkmate-sponsored Phase 1b dose escalation and expansion studies:

1. CMP-001-001: A Multicenter, Open-Label, Phase 1b Clinical Study of CMP-001 Administered Either in Combination With Pembrolizumab or as Monotherapy in Subjects With Advanced Melanoma (IT route of administration [ROA])

2. CMP-001-002: A Multicenter, Two Part, Phase 1b Study Evaluating Alternative Routes of Administration of CMP-001 in Combination With Pembrolizumab in Subjects With Advanced Melanoma (SC and SC/IT ROA)

3. CMP-001-003: A Multicenter, Two-Part, Phase 1b Clinical Study of CMP-001 in Combination With Atezolizumab With and Without Radiation Therapy in Subjects With Advanced Non-Small Cell Lung Cancer (NSCLC) (SC/IT ROA)

A total of 255 subjects have received at least 1 dose of CMP-001 in 3 Checkmate-sponsored studies as of 01 June 2020, including 226 subjects with advanced melanoma who received CMP 001 as monotherapy or in combination with pembrolizumab, and 29 subjects with NSCLC who received CMP 001 in combination with atezolizumab with or without radiation therapy. CMP-001 has also been combined with other PD-1 blocking antibodies (nivolumab, atezolizumab, avelumab).

In the 3 Checkmate-sponsored studies (with the exception of the CMP-001 monotherapy arm in Study CMP-001-001 Part 2), treatment-emergent adverse events ([TEAEs], defined as an adverse event [AE] that started or worsened in severity on or after the date that study treatment was first administered), are assessed in relation to study treatment and are not attributed individually to CMP-001, pembrolizumab, atezolizumab, or radiation therapy. In all future Checkmate-sponsored studies, relationship of an AE will be assessed to each of the individual components of the study treatment.

1.1.1 Clinical Safety & Clinical Efficacy

Study CMP-001-001

As of 01 June 2020, 199 subjects have received CMP-001 IT at doses ranging from 1 mg to 10 mg in combination with pembrolizumab or as monotherapy in Study CMP-001-001. Some subjects received CMP-001 SC per protocol.

Part 1: CMP-001 in Combination with Pembrolizumab

In the Part 1 Dose Escalation and Dose Expansion portion of the study, 159 subjects received at least 1 dose of CMP-001 IT at starting doses ranging from 1 mg to 10 mg in combination with pembrolizumab IV on 2 different dosing schedules. The median duration of treatment with CMP 001 (includes subjects currently on and off treatment) for the 159 subjects in the Part 1 is 2.4 months (range: 0 to 47 months).

For the combined Part 1 Dose Escalation and Part 1 Dose Expansion Phases of Study CMP 001 001 (N=159), the most commonly occurring TEAEs (all causality TEAEs occurring in at least 20% of subjects) for CMP 001 in combination with pembrolizumab by highest incidence were chills, pyrexia, fatigue, nausea, vomiting, headache, injection site pain, diarrhoea, decreased appetite, back pain, hypotension, and constipation. Twenty-seven (17.0%) subjects experienced a serious adverse event (SAE) assessed as related to study treatment. Treatment-related SAEs reported in more than 1 subject include hypotension (7 subjects; 4.4%) and pyrexia, muscular weakness and cytokine release syndrome (2 subjects, each event; 1.3 %).

A total of 16 (10.1%) subjects discontinued study treatment due to a TEAE. Treatment-related TEAEs that led to discontinuation included pneumonitis (2 subjects) and dyspnoea, pancreatitis, chills, disseminated intravascular coagulation, diarrhoea, generalised oedema, atrial fibrillation, and muscular weakness (1 subject, each event).

There have been 4 fatal SAEs in Part 1 of Study CMP-001-001: 2 events of respiratory failure, 1 event of sepsis, and 1 event of death, not otherwise specified. None of the deaths are considered related to study treatment.

Part 2: CMP-001 Monotherapy

In Part 2 Monotherapy, 40 subjects received at least 1 dose of CMP-001 IT at starting doses of 5 mg or 10 mg on 1 dosing schedule. The median duration of treatment with CMP 001 (includes subjects currently on and off treatment) for the 40 subjects in the Part 2 is 1.7 months (range: 1 to 21 months).

The most commonly occurring TEAEs (all causality TEAEs occurring in at least 20% of subjects) in Part 2 Monotherapy by highest incidence were nausea, chills, pyrexia, headache, fatigue, hypotension, oedema peripheral, back pain, constipation, decreased appetite, diarrhoea, vomiting, hypertension, and pruritus. Serious AEs assessed as related to CMP-001 were reported in 6 (15%) subjects. Treatment-related SAEs that occurred in more than 1 subject included hypotension (3 subjects; 7.5%). Treatment-related SAEs that led to discontinuation of study drug included bradycardia, hypotension, and presyncope (in 1 subject); headache, nausea, and chills (in 1 subject); and injection site reaction (1 subject).

No TEAEs with an outcome of death have been reported in Part 2 monotherapy.

Part 2 Crossover

In Part 2 Monotherapy Crossover (CMP-001 in combination with pembrolizumab), 15 of the 40 subjects from Part 2 Monotherapy crossed over to receive at least 1 dose of CMP-001 in combination with pembrolizumab after PD was observed and documented.

In Part 2 Monotherapy Crossover (CMP-001 in combination with pembrolizumab), the most commonly reported (all causality TEAEs occurring in a least 20% of subjects) by highest incidence were chills, pyrexia, injection site pain, hypertension, constipation, and cough. One subject had an SAE reported as death (not otherwise specified) that was assessed by the Investigator as not related to study treatment.

Study CMP-001-002

As of 01 June 2020, in the Part 1 Dose Escalation Phase of Study CMP-001-002, 27 subjects have received at least 1 dose of CMP-001 by SC injection at doses ranging from 5 mg to 17.5 mg in combination with pembrolizumab.

The most commonly occurring TEAEs (all causality TEAEs occurring in at least 20% of subjects) for CMP-001 in combination with pembrolizumab by highest incidence were fatigue, nausea, diarrhoea, hypertension, arthralgia, chills, and rash. Serious AEs assessed as related to study treatment were tumor pain and erythema multiform (1 subject, each event). No subjects discontinued study treatment because of a treatment-related TEAE. No TEAEs with an outcome of death have been reported.

Study CMP-001-003

Part A Stage 1

In Part A Stage 1 of Study CMP-001-003, 13 subjects with advanced NSCLC received at least 1 dose of CMP 001 SC or IT in combination with atezolizumab IV.

The most commonly occurring TEAEs (all causality TEAEs occurring in at least 20% of subjects) for CMP-001 in combination with atezolizumab in Part 1 by highest incidence were pyrexia, hypotension, chills, fatigue, decreased appetite, nausea, back pain, headache, dyspnea, platelet count decreased, anaemia, hyponatraemia, hypophosphataemia, pneumonia, and rash. A total of 9 (69.2%) subjects have experienced at least 1 SAE. SAEs assessed as treatment-related occurred in 4 subjects and included pyrexia, flushing, and hypotension (in 1 subject); chills, pyrexia, and tachycardia (in 1 subject); brain oedema, mental status changes, and fatigue (in 1 subject); and pneumonitis and diabetes mellitus (in 1 subject).

One subject discontinued study treatment in Part A due to a non-fatal SAE of Grade 3 pneumonitis that was assessed by the Investigator as related to study treatment. There were no deaths reported in Part A of the study.

Part B Stage 1

In Part B Stage 1 of the study, 16 subjects received radiation and at least 1 dose of CMP-001 in combination with atezolizumab.

The most commonly occurring TEAEs (all causality TEAEs occurring in at least 20% of subjects) for subjects receiving radiation and at least 1 dose of CMP-001 in combination with atezolizumab includes anaemia, pyrexia, hypotension, chills, decreased appetite, hypokalaemia, hypophosphataemia, nausea, fatigue, and platelet count decreased. A total of 9 (56.3%) subjects experienced at least 1 SAE including 7 subjects who experienced an SAE that was assessed as related to study treatment. Treatment-related SAEs included hypotension, blood bilirubin increased, and

anaemia (in 1 subject); hypotension and flushing (in 1 subject); vomiting, pyrexia, nausea, hypotension, chills, and tachycardia (in 1 subject); and hypotension, atrial flutter, sepsis, asthenia (each occurring in 1 subject). There was 1 fatal SAE of cardio-respiratory arrest, which was considered unrelated to treatment by the Investigator. No subjects discontinued study treatment because of a treatment-related TEAE.

The most frequently reported TEAEs with CMP-001 + other agents can be found in the CMP-001 Investigator Brochure.

Analysis of Safety Data to Date

In the 3 Checkmate-sponsored studies (with the exception of the CMP-001 monotherapy arm in Study CMP-001-001 Part 2), TEAEs are assessed in relation to study treatment and are not attributed to the individual components, CMP-001, pembrolizumab, atezolizumab, or radiation therapy. There is no evidence to suggest that CMP-001 monotherapy or CMP-001 in combination with pembrolizumab, atezolizumab, or atezolizumab with radiation therapy, increases the frequency or severity of immune related AEs.

Analysis of safety data demonstrates a similar safety profile for all 3 Checkmate-sponsored studies in patients with cancer that predominately consists of Grade 1 and Grade 2 AEs. Commonly reported TEAEs (occurring in 20% or more subjects) that have been observed across these clinical studies with CMP-001 were chills, pyrexia, fatigue, hypotension, nausea, and vomiting. The frequency of AEs that are Grade 3 or higher peaks with the third to sixth injections of CMP-001.

Based on the SAEs reported in 255 subjects treated with CMP-001 to date, expected events are hypotension (17 subjects; 6.7%), pyrexia (7 subjects; 2.8%), and cytokine release syndrome (3 subjects, 1.2%). All other SAEs were seen in 2 or fewer (1% or less) subjects.

Clinical Efficacy

All statements related to data and all data summaries are based on data entered into the study-specific EDC systems as of 01 June 2020 for the 3 Checkmate-sponsored studies.

Data for the intent-to-treat analysis set for each study, defined as all subjects receiving at least 1 dose of CMP-001, are based on Response Evaluation Criteria for Solid Tumors version 1.1 (RECIST v1.1) by Investigator assessment.

Study CMP-001-001

Preliminary efficacy data for the combined Part 1 Dose Escalation and Part 1 Dose Expansion Phases of the ongoing Study CMP-001-001 included responses in subjects who received CMP 001 at doses ranging from 3 mg to 10 mg in combination with pembrolizumab. The protocol-specified efficacy endpoint of best objective response

rate (ORR) was 18.9% (30 of 159 subjects; 95% CI = 13.1%, 25.9%) and included 8 CRs and 22 PRs. The best ORR including post-progression responders (n=7) was 23.3% (37 of 159 subjects; 95% CI = 17.0%, 30.7%). There were 35 (22.0%) subjects with a RECIST best response of stable disease (SD), 74 (46.5%) subjects with a RECIST best response of PD, and 13 (8.2%) subjects who discontinued prior to having a post-baseline scan. The median duration of response (DOR) for the 30 RECIST responders was 13.9 months.

Subjects treated at the CMP-001 10 mg dose administered QW for 7 weeks and Q3W thereafter (ie, the recommended Phase 2 dose [RP2D]) had a best ORR of 23.0% (14 of 61 subjects; 95% CI = 13.2%, 35.6%) and included 3 CRs and 11 PRs. The best ORR including post-progression responders (n = 3) was 27.9% (17 of 61) subjects; 95% CI = 17.2%, 40.9%).

Preliminary efficacy data for the Part 2 CMP-001Monotherapy Arm of Study CMP-001-001 included a best ORR of 17.5% (7 of 40 subjects; 95% CI = 7.3%, 32.8%). All responders had a PR. Best response for the remaining subjects included 13 (32.5%) subjects with SD and 20 (50.0%) subjects with progressive disease (PD).

Based upon these data, 10 mg CMP-001 IT administered QW for 7 weeks and Q3W thereafter in combination with a PD-1 blocking antibody was chosen as the RP2D.

Study CMP-001-002

Preliminary efficacy data for the 25 evaluable subjects in the ongoing Part 1 Dose Escalation Phase of Study CMP-001-002 included a best ORR of 8.0% (2 of 25 subjects; 95% CI = 1.0% to 26.0%) and included best responses of 1 CR and 1 PR, both in the 10 mg SC dose group. Eight (32.0%) subjects had a RECIST best response of SD, 11 (44.0%) subjects had a RECIST best response of PD, and 4 (16.0%) subjects discontinued prior to having a post baseline tumor assessment. Two of the 27 subjects dosed were pending their first post baseline scan at the time of data cutoff and are not evaluable for response.

Study CMP-001-003

In the completed Study CMP-001-003 in subjects with NSCLC who had progressed on prior PD 1/PD-L1 therapy, no RECIST responses were observed in 13 subjects in Part A Stage 1 and 16 subjects in Part B. This study was stopped after interim analysis at the conclusion of Stage 1 and all data are final. In Part A of the study, 3 (23.1%) subjects had a RECIST best response of SD, 8 (61.5%) subjects had a RECIST best response of PD, and 2 (15.4%) subjects discontinued from the study before having a post-baseline tumor assessment. In Part B of the study, 8 (50.0%) subjects had a RECIST best response of SD, 5 (31.3%) subjects had a RECIST best response of PD, 3 (18.8%) subjects discontinued prior to post-baseline follow-up scans; 1 of these 3 subjects had an incomplete follow-up scan and was not evaluable per RECIST.

CMP-001 Clinical Safety and Efficacy Summary

CMP-001 is an immune activator that consists of a CpG-A ODN (G10) contained within a recombinantly-expressed protein capsid as carrier (Qb). The postulated mechanism of action after IT or SC injection includes local uptake by pDCs in the tumor and tumor-draining lymph nodes. Upon uptake, the Qb capsid enters an endosome where the G10 CpG-A ODN is released from the CMP-001 VLP and stimulates TLR9 in pDC, inducing the production of large amounts of type I IFN, and promoting a Th1 type immune response with the generation of large numbers of anti-tumor CD8+ T cells able to traffic systemically to distant metastatic sites.

In the ongoing Checkmate-sponsored Studies CMP-001-001 and CMP-001-002, and the completed Checkmate-sponsored Study CMP-001-003, preliminary analysis of CMP-001 safety data in 255 subjects who have received at least 1 dose of CMP-001 in combination with a PD 1/PD-L1 blocking antibody or as monotherapy demonstrates a safety profile that predominantly consists of Grade 1 to Grade 2 AEs, including fever (pyrexia), chills, nausea, vomiting, diarrhoea, headache, rash, and hypotension.

Preliminary efficacy data for the Part 1 Dose Escalation and Part 1 Dose Expansion Phases of Study CMP-001-001 in subjects with advanced melanoma included a best ORR of 18.9% per RECIST and 23.3% for RECIST and post-progression responders. Subjects treated at the RP2D (CMP-001 10 mg dose administered QW for 7 weeks and Q3W thereafter) had a best ORR of 23.0%. Responses included CRs and PRs. The median DOR for the RECIST responders was 13.9 months and 19.9 months when including post-progression responders. Preliminary efficacy data for the Part 2 CMP-001 Monotherapy Arm included a best ORR of 17.5% with all responders having a PR.

Preliminary efficacy data for the Part 1 Dose Escalation Phase of Study CMP-001 002 in subjects with advanced melanoma included a best ORR of 8.0%, with 1 CR and 1 PR.

Final efficacy data from Study CMP-001-003 in subjects with advanced NSCLC who had progressed on prior PD-1/PD-L1 therapy included no RECIST responders in the 13 subjects in Part A Stage 1 and 16 subjects in Part B Stage 1 of the study.

1.1.2 CMP-001 Potential Autoimmunity

The potential of CMP-001 to induce anti-dsDNA antibodies is considered very low. The ODN G10 is not readily visible to the B cell receptor as it is encapsulated by a spherical particle. Accordingly, a clinically relevant increase in anti-dsDNA antibodies or antinuclear antibodies, or clinical evidence of autoimmunity, was not detected in any of the patients treated with CMP-001 after follow-up times of 1 to 2 years. Induction or exacerbation of autoimmune diseases is not expected for CMP-001

because this has not been observed previously with other TLR9 agonists administered for longer periods of time at higher dosages. Patients with a diagnosis of systemic autoimmune diseases were excluded from prior clinical studies of CMP-001. All enrolled patients were monitored for induction of antinuclear (ANA) and anti-dsDNA antibodies. No clinical signs indicative for autoimmune disease have been reported to date.

Early hypotheses that exposure to DNA containing CpG motifs generally induce autoimmunity have proven unfounded (Krieg and Vollmer 2007, Krieg, 2012). Nevertheless, in some mouse models of autoimmunity, CpG oligonucleotide treatment exacerbated disease, while in others it prevented autoimmune or inflammatory disease (Krieg and Vollmer 2007). In addition, as TLR9 signaling is involved in the immune defense mechanisms against bacteria, several feedback suppression mechanisms have evolved to regulate TLR9 activity such as expression of indoleamine 2,3- dioxygenase (IDO), cyclooxygenase-2, suppression of cytokine signaling, etc. In accordance, the clinical experience to date indicates that CpG ODN treatment of healthy humans, cancer patients, or individuals infected with HIV or HCV does not readily induce early markers of autoimmune disease (Krieg, 2012).

1.1.3 CMP-001 Potential Effects Related to IFNα Induction

In consideration of the postulated mode of action through stimulation of Th1 cytokines, the occurrence of symptoms as described for therapeutic use of IFNα should be considered. Elevated body temperature and fever, shivering, feeling cold, headache, and myalgia are potential adverse events, which might be attributed to stimulation of cytokines by QbG10. The incidence of such symptoms was generally low. With B cell vaccines which use the native Qb capsid (containing bacterial RNA instead of a CpG) to induce specific antibodies against various targets, such reactions had a higher incidence showing that the CpG component in QbG10 and associated induction of IFNα hardly contribute to these symptoms (Ambuhl et al., 2007; Cornuz et al., 2008; Kundig et al., 2006; Maurer et al., 2005; Tissot et al., 2010). Symptoms of systemic reactogenicity would usually appear within 6-8 hours after the second and subsequent injections (once the anti-Qb antibody response had been induced), and usually disappear within 24 hours and respond well to usual doses of acetaminophen, if required.

Other symptoms frequently observed after therapeutic doses of IFNα such as gastrointestinal symptoms, depression, dermatological symptoms and cardiovascular disorders were rarely reported after QbG10 as well as after placebo and considered not of suspected relationship.

No IFNα could be detected 12 h and 24 h after injection in sera of subjects treated with 0.3 mg QbG10 (detection limit 39 pg/mL). In contrast, IFNα serum levels after therapeutic doses of recombinant IFNα are in the ng/mL range (e.g., Pegasys®, Roche; Intron A®, Schering).

1.1.4 CMP-001 Potential Drug Interactions

Pharmacokinetic interactions between the CMP-001 and anti-OX40 antibodies are not expected.

INCAGN01949 (OX40 Agonist) Background

INCAGN01949 is a fully human monoclonal antibody with an IgG1 heavy chain and κ light chain, expressed by recombinant DNA technology in a CHO cell line. INCAGN0149 has two potential mechanisms of actions. It can stimulate T cell proliferation by engagement of the OX40 receptor on T effector populations or eliminate T regulatory cells through an ADCC mechanism as an IgG1 antibody.

INCAGN01949 binds selectively to the extracellular domain of human OX40 with a KD of 0.12 nM. INCAGN01949 functions as an OX40 agonist antibody in human cells, activating NFκB signaling and providing T cell costimulation in the context of suboptimal TCR activation. INCAGN01949 has the ability to increase T cell function.

Two clinical studies are ongoing, and 136 participants have been exposed to at least 1 dose of INCAGN01949 by intravenous drug administration. Study INCAGN 1949-101 is a Phase 1/2, open-label, dose-escalation, safety and tolerability study in participants with advanced or metastatic solid tumors. Study INCAGN 1949-201 is a Phase 1/2, open-label, nonrandomized study to determine the safety, tolerability, and efficacy of INCAGN01949 when given in combination with immune therapies (nivolumab and ipilimumab).

In both studies, following a single 30-minute IV infusion of escalating doses (7 to 1400 mg), the disposition of INCAGN01949 was biphasic with mean plasma half-life values ranging from 140 to 391 hours. The estimated mean plasma clearance following single dose administration was low, which is typical for a monoclonal antibody. The estimated mean volume of distribution ranged from 3240 to 9900 mL, which is also consistent with expectations for a monoclonal antibody. Following repeated Q2W administration, the preinfusion serum concentrations for the 7, 20, 70, 200, and 700 mg dose cohorts increased with each subsequent cycle, suggesting lack of any ADA effect on the PK of INCAGN01949.

Preliminary data indicate absence of any ADAs in both studies. Analysis of proinflammatory cytokines revealed no dose-related changes in plasma cytokines and inflammatory proteins in participants infused with doses up to 350 mg consistent with the lack of infusion reactions with drug administration. No major changes were observed among participants infused with doses up to 1400 mg in the frequency of immune cell populations that were evaluated.

In Study INCAGN 1949-101, 84 participants have received INCAGN01949 doses of 7, 20, 70, 200, 350, 700, or 1400 mg IV Q2W. No DLTs were reported. The most common TEAEs (> 10%) for INCAGN01949 monotherapy were fatigue, decreased

appetite, constipation, cough, nausea, abdominal pain, diarrhea, dyspnea, vomiting, and back pain.

In Study INCAGN 1949-201, 36 participants have received INCAGN01949 IV doses of 70, 200, 350, or 700 mg Q2W + nivolumab 240 mg Q2W. The most common TEAEs (> 10%) for INCAGN01949 + nivolumab were fatigue, pruritus, abdominal pain, back pain, cough, peripheral edema, arthralgia, decreased appetite, diarrhea, nausea, anemia, vomiting, amylase increased, headache, lipase increased, and pyrexia.

There were no new toxicities observed with the administration of INCAGN0149 in combination with nivolumab or ipilimumab nor was the rate of immune-related adverse events increased compared with the administration of nivolumab or ipilimumab alone.

There was one objective tumor response in a patient with gallbladder cancer with INCAGN01949 alone. The response rate of the combinations of INCAGN01949 with nivolumab was not increased compared with single agent nivolumab or ipilimumab.

The current study will use once a week schedule of administration and will also be the first evaluation of INCAGN01949 as an intratumoral injection. It is not anticipated that there will be a major change in toxicity with this approach but subjects will be closely monitored for systemic and local reactions. For safety purposes the starting IT dose will be only 500mcg/m2 which is less than 10% of the highest dose administered IV.

1.1.5 Potential Risks of INCAGN01949 (OX40 agonist)

The occurrence of DLTs and other toxicities (related or unrelated to INCAGN01949) will guide decisions for treatment interruptions and discontinuation for individual participants. For management of DLTs or other urgent situations that may arise during treatment with INCAGN01949, in all cases, investigators may employ any measures or concomitant medications, after discussion with the sponsor (whenever possible), necessary to optimally treat the participant.

Participants with potential irAEs should receive appropriate supportive care measures as deemed necessary by the treating investigator.

The most frequently reported TEAEs with INCAGN01949 + other agents can be found in the INCAGN01949 Investigator Brochure.

2.0 HYPOTHESIS

We hypothesize that activating the innate and adaptive immune systems, via in-situ vaccination, will make pancreatic and potentially other cancers recognizable to the immune system. Pancreatic cancer has historically not responded well to immuno-oncology agents but we believe this immunoenhancing technique will induce an antitumor T cell response throughout the body, which will attack both local and metastatic tumors.

3.0 OBJECTIVES

Primary Objective

Phase IB

To determine the maximum tolerated dose and tolerance of CMP-001 (TLR9 agonist) in combination with INCAGN01949 (an activating antibody against OX40) both given intratumorally for patients with previously treated (for their metastatic disease) pancreatic ductal adenocarcinoma and other types of cancer except melanoma.

Phase II
To determine the efficacy (Disease control rate of CR+ PR+SD X 16 weeks) of CMP-001 (TLR9 agonist) in combination with INCAGN01949 (anti-OX40 antibody) for patients with previously treated (for their metastatic disease) pancreatic ductal adenocarcinoma.

To determine effects on tumor markers.

Secondary Objective

- Define the toxicity of the combination of CMP-001 (TLR9) + INCAGN01949 (OX40)

- Determine progression free survival and overall survival

Exploratory Objectives

- Using flow cytometry on peripheral blood OX40 expression will be analyzed within the lymphocyte subsets (Teff and Treg)

- On tissue samples collected prior to, and during, treatment, we will:

- Use flow cytometry to enumerate CD4+ and CD8+ T cell subsets, and the expression of activation/differentiation markers (including CD127, HLA-DR, CD45RO, CCR7, CXCR3) on each
- Use RT-PCR and sequencing to amplify and characterize the TCRa and b sequences of tumor-infiltrating T cells, looking for evidence of oligo-clonal T cell expansion, OX40 expression
- If there is adequate tumor tissue, perform RNAseq to determine different immune cell populations, including T cells and macrophages

Primary Endpoints

- Phase IB – Dose and tolerance and recommended Phase II dose
- Phase II – Disease control rate (CR+PR+SD x 16 weeks via RECIST and iRECIST) and effects on tumor markers

Secondary Endpoints

- Incidence of toxicities
- Progression free and overall survival

Exploratory Endpoints

- To determine OX40 expression within the lymphocyte subsets (Teff and Treg)
- On tissue samples collected prior to, and during, treatment, we will:
    - Use flow cytometry to enumerate CD4+ and CD8+ T cell subsets, and the expression of activation/differentiation markers (including CD127, HLA-DR, CD45RO, CCR7, CXCR3) on each
    - Use RT-PCR and sequencing to amplify and characterize the TCRa and b sequences of tumor-infiltrating T cells, looking for evidence of oligo-clonal T cell expansion, OX40 expression
    - If there is adequate tumor tissue, perform RNAseq to determine different immune cell populations, including T cells and macrophages

4.0 PATIENT ELIGIBILITY

4.1 Eligibility

A total of up to 21 patients in Phase IB and up to 21 in Phase II with previously treated stage IV pancreatic cancer and other appropriate types of metastatic cancer except melanoma will be recruited from up to 4 centers.

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

4.1.1 Inclusion Criteria

Patients must meet the following criteria to be included in the trial:

1. Be willing and able to provide written informed consent for the trial.

2. Be ≥ 18 years of age.

3. Histologically or cytologically confirmed pancreatic adenocarcinoma with metastasis or other locally advanced un-resectable solid tumor malignancies (during the phase Ib and pancreatic cancer during phase II) deemed appropriate by the Investigator except melanoma.

4. Patients will have had at least 2 prior therapies for locally advanced, un-resectable and/or metastatic disease. Adjuvant therapy will count as one line of therapy if disease progression occurred during treatment or within 6 months of completion.

   Patients with metastatic pancreatic cancer must have received either FOLFIRINOX or a gemcitabine-based regimen as one of their prior lines of therapy. Patients with germline BRCA mutations must have received olaparib as maintenance therapy.

5. Be willing to undergo an image-guided biopsy of a tumor lesion at baseline, after 2 weeks of IT injection and 4 weeks of IT injection (week 4 and 6), unless tumor is considered inaccessible or biopsy is otherwise considered not in the patient's best interest.

6. Have a performance status of 0 or 1 on the ECOG performance scale.

7. Subjects must have at least one extra-central nervous system (CNS), non-bone tumor lesion amenable for IT injection ≥ 1.5 cm and that is not in close proximity or encasing crucial structures such as major blood vessels, trachea, nerve bundles etc. Measurable disease is required in a minimum of two lesions and

there must be at least one measurable lesion in addition to the one being injected.

8. Demonstrate adequate organ function as defined below in Table 2.

9. Female participants of childbearing potential should have a negative serum pregnancy test within 24 hours prior to receiving first dose of trial medication.

10. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

    a. Not a woman of childbearing potential (WOCBP)
    - A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:
        - Has not undergone a hysterectomy or bilateral oophorectomy; or
        - Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

    OR

    b. A WOCBP who agrees to follow the contraceptive guidance during the treatment period and for at least 180 days after the last dose of trial treatment.

11. Male participants must agree to use contraception as detailed in the full protocol during the treatment period and for at least 120 days after the last dose of trial treatment and refrain from donating sperm during this period.

Table 4. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1.5 x 10^9/L
Platelets	≥100 x 10^9/L
Hemoglobin	≥9 g/dL without transfusions within 7 days of assessment (transfusions are allowed prior to this period)
Renal	
Serum creatinine OR Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) OR ≥60 mL/min for subject with creatinine levels 〉1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN OR
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN OR ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation*	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 X ULN NOTE: Low molecular weight heparin at full dose or prophylactic dose is allowed as long as the treating physician deems it safe to hold the LMWH on the day before and the day of the intra-tumoral injection. No other anti-coagulants are permitted.
[a] Creatinine clearance should be calculated per institutional standard. * Because of the intratumor injections patients cannot be on any anticoagulants other than LMWH.	

4.1.2 Exclusion Criteria

Patients ***must not meet any*** of the following criteria in order to be eligible for the trial:

1. Hypersensitivity to CMP-001 (TLR9 agonist) or INCAGN01949 (anti-OX40) or any of its excipients.

2. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to Week 1/Day 1, or who has not recovered (i.e., ≤ Grade 1 or to baseline) from adverse events due to agents administered more than 4 weeks earlier.

3. Has had prior chemotherapy, investigational agent, targeted small molecule therapy, or radiation therapy within 3 weeks (or 5 half-lives whichever is shorter) prior to Week 1/ Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent(s).

Note: Patients with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the trial.

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

4. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer. Other malignancies which have been treated with curative intent, or for which patients are not receiving active therapy, may be considered upon discussion with the Investigator.

5. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. Use of prophylactic anti-epileptic drugs is permitted. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.

6. 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 (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment; these patients may receive stress steroids orally or IV before the procedure.

7. Has history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

8. Has an active bacterial infection requiring systemic therapy.

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

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

11. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

12. Has a known history of or is positive for Hepatitis B (e.g., HBsAg reactive) or untreated Hepatitis C. Treated Hepatitis C with sustained virologic response, and patients who are negative for Hepatitis BsAg are not excluded.

13. Current, serious, clinically significant cardiac arrhythmias as determined by the treating investigator.

14. Has received a live vaccine within 30 days of planned start of trial therapy.

    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

15. Patients must not be receiving any anticoagulation. Low molecular weight heparin at full dose or prophylactic dose is allowed as long as the treating physician deems it safe to hold the LMWH on the day before and the day of the intra-tumoral injection.

16. Patients should not be on aspirin or any anti-platelet agent. Patients may have been receiving aspirin 81 mg if deemed safe by the investigator to hold aspirin for the duration of the study, starting at least 7 days prior to start of treatment.

5.0 TRIAL TREATMENTS

The treatments to be used in this trial are outlined below in Table 3. Full details for dose preparation and administration are in the pharmacy manual.

Table 5. Trial Treatments

Drug	Dose/Potency	Dose Frequency	Route	Regimen/Treatment Period
CMP-001 (TLR9)	A fixed dose of 10mg CMP-001 will be used for IT injection (5mg will be used for the first two SC injections).	Once a week for 6 weeks	First two doses are SC and remaining 4 doses are IT	Week 1, Day 1 (SC) Week 2, Day 1 (SC) Week 3, Day 1 (IT) Week 4, Day 1 (IT) Week 5, Day 1 (IT) Week 6, Day 1 (IT)
INCAGN01949 (OX40)	Up to 6 different dose levels (up to 6 patients per dose level in Phase IB to select dose level for Phase II) 500 mcg/m^{2**} 1000 mcg/m^2 1670 mcg/m^2 2505 mcg/m^2 3507 mcg/m^2 4559 mcg/m^{2*}	Once a week for 4 weeks	All doses are IT	Week 1, Day 1 (none) Week 2, Day 1 (none) Week 3, Day 1 (IT) Week 4, Day 1 (IT) Week 5, Day 1 (IT) Week 6, Day 1 (IT)

5.1.1 Body Surface Area Calculation

The calculation of the dose of INCAGN01949 (OX40) will be based on the patient's body surface area (BSA) using the Mosteller formula (Verbraeken 2006). The BSA will be calculated at baseline and before each new week, based on the actual height and weight of the patient. If there has been a ≥10% weight change from baseline, the drug doses will be recalculated based on the new BSA value. The calculated dose will be rounded to the nearest whole microgram (mcg).

5.1.2 Dose Escalation in Phase IB

The dose escalation scheme proposed is a conservative modified Fibonacci method (Le Tourneau 2009).

Up to six dose levels of INCAGN01949 (OX40) as detailed in Table 3 are planned in order to determine the MTD for dose selection for the Phase II trial. One patient will be entered at each dose level until the occurrence of a grade $\geq$ 2 treatment related toxicity, then a minimum of 3 patients will be entered at each dose level starting at the dose level with the grade 2 treatment related toxicity.

The starting dose for intratumoral injection of INCAGN01949 is based on the known safety profile of intravenous INCAGN01949 at doses ranging from 7-1400 mg. The proposed starting dose is less than 10% of the intravenous route of administration and provides an additional margin for safety in the trial. There is the potential for OX40 upregulation following TLR9 agonist administration and its binding could produce cytokine release.

One or three patients at a given dose level will then be followed for a minimum of 4 weeks before initiating dosing at the next level. If any patient experiences a DLT, up to an additional 3 patients will be added at that dose level. All patients will be followed through the first 4 doses (Weeks 1-4 of dosing, including CMP-001 SC alone for 2 doses, and CMP-001 IT plus INCAGN01949 IT for 2 doses) before further dose escalation occurs. If no more than 1 of 6 develops a DLT, dose escalation will continue to the next level for the succeeding patients. However, if another patient experiences a treatment related toxicity qualifying as a DLT, those doses will be considered the toxic doses. The MTD will then be defined as the next lower dose level.

If 2 of 6 patients in dose level 1 develop DLTs, further patients will be enrolled into dose level -1 for CMP-001 (5mg) and INCAGN01949 of 250mcg/m2. If 2 or more patients experience any DLT attributable to the study drugs at dose level -1, study accrual will be stopped, and all toxicities will be reviewed.

The design will allow us to determine the MTD. However, the RP2D may be different and take into account pharmacodynamics markers such as expression of OX40 on the CD4+ T cells.

5.1.3 Dose Modification for Toxicity

Toxicities will be graded using the NCI-CTCAE V5.0 (appendix 1). If toxicity occurs during or after any treatment, the toxicity will be graded and appropriate supportive care treatment will be administered to decrease the signs and symptoms (e.g. antiemetics, antidiarrheals, antipyretics, antihistamines).

Dose adjustments will be made according to the table below. A maximum of two dose reductions will be allowed. Further toxicities requiring dose reduction will result in study discontinuation.

In most cases, management of toxicity may require either a temporary or permanent discontinuation of both CMP-001 and INCAGN01949. 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 Sponsor consultation and approval.

Dosing Modifications and Toxicity Management Guidelines

CTC Grade	Dose Modification	Toxicity Management
Any Grade	NOTE: Dose modifications are not required for adverse events not deemed to be related to study treatment (i.e. events due to underlying disease) or laboratory abnormalities not deemed to be clinically significant.	Treat accordingly as per institutional standard.
1	No dose adjustment.	
2	Continue treatment and increase monitoring frequency to once weekly at a minimum until the event returns to ≤ Grade 1.	
3-4 **First Occurrence**	Hold study treatment until resolution to ≤ Grade 1 or baseline. Then resume therapy at one level dose reduction. If patient is receiving the lowest dose level of study drug and experiences a treatment-related Grade 3-4 adverse event, then treatment will be permanently discontinued. For toxicities with adequate supportive care options such as nausea, vomiting, diarrhea, the Grade 3 toxicity must have occurred despite optimal supportive care to warrant a dose reduction.	
3-4 **Second Occurrence**	Discontinue study treatment permanently if patient has a recurrent Grade 3-4 toxicity despite optimal supportive care.	

NOTE:
- For Grade 3-4 electrolyte abnormalities, if easily managed medically and return to Grade ≤ 2 within 72 hours, do not require a dose reduction.
- For Grade 3-4 laboratory abnormalities, the decision to discontinue treatment should be based on accompanying clinical signs/symptoms and as per Investigator's clinical judgment and in consultation with the sponsor.

Dose Levels of CMP-001 and INCAGN01949

Dose Level	CMP-001 (mg)	INCAGN01949 (mcg/m^2)
-1	5 (IT)	250 (IT)
1	10 (IT)	500 (IT)
2	10 (IT)	1000 (IT)
3	10 (IT)	1670 (IT)
4	10 (IT)	2505 (IT)
5	10 (IT)	3507 (IT)
6	10 (IT)	4559* (IT)

* If higher dose levels are needed, escalation will be in 50% increments

5.1.4 Injection Site Reactions

If subjects develop inflammation at the injection site of CMP-001 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.

5.1.5 Required Prophylaxis Before and After CMP-001 Dosing

CMP-001 has been administered as an IT or SC injection. Intratumoral injection of CMP-001 provides the most direct approach to activate tumor-associated pDC, and thereby may induce a more potent antitumor CD8+ T-cell response.

To reduce the severity of these symptoms associated with CMP-001 treatment, prophylaxis is required. Prophylactic regimens already in place at institutions should be followed; if not, below is a suggested regimen that has been effective for the treatment of CMP-001 induced AEs:

- Intravenous fluids (eg, approximately 1000 cc IV normal saline)
- Anti-pyretics (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

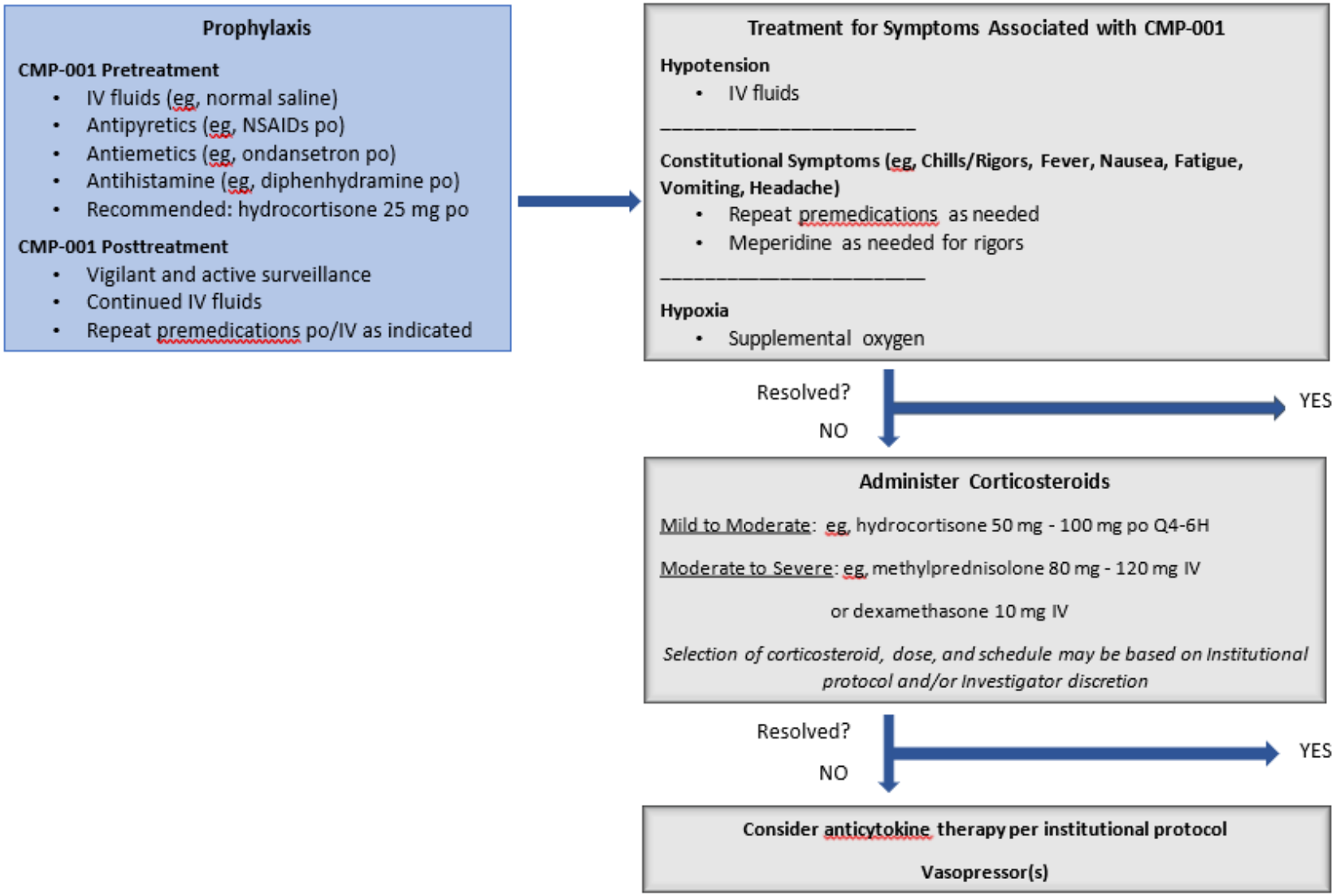
receive stress dose steroids (ie, 50 to 100 mg hydrocortisone orally every 8 hours) prior to or immediately after injection of CMP-001.

Prophylaxis administration should be completed before initiation of CMP-001 injection. The medications are recommended for oral administration, but IV is acceptable at the discretion of the investigator. It is also highly recommended to continue to administer fluids immediately following the CMP-001 injection, rather than waiting to initiate fluids if hypotension is detected. There is no waiting period between the end of prophylaxis and the start of the CMP-001 injection. The following algorithm (**Figure 2**) is provided as guidance for the treatment of symptoms associated with CMP-001.

In subjects with hypotension unresponsive to supportive care with intravenous fluids, the administration of stress dose steroids is recommended according to institutional practices. Additional treatment measures may include the use of anti-cytokine therapy per institutional protocol. Prior to dosing an anti-cytokine therapy, it is recommended that blood be obtained to determine the cytokine level believed to be responsible for the AE. The result of the cytokine assay does not need to be available prior to dosing.

For subjects who previously experienced a CMP-001-related Grade 3 or higher AE, prophylaxis with stress dose steroids (50 mg to 100 mg hydrocortisone orally every 8 hours before or immediately after injection of CMP-001 or institutional standard) is recommended for subsequent CMP-001 doses. A minimum dose of corticosteroids of 25 mg prednisone or equivalent (eg, hydrocortisone, methylprednisolone, dexamethasone) is recommended. The selection and dose of corticosteroid should be determined by the Investigator based on clinical parameters.

Figure 2: Treatment Algorithm for Management of Adverse Events Associated with CMP-001



5.1.6 Dose Limiting Toxicity

DLT (dose Limiting toxicity): DLT will be assessed in the first 28 days of dosing. To be evaluable for DLT, patient must have either experienced a DLT or received all scheduled doses of therapy in the first 4 weeks of treatment. Patients who have treatment held or discontinued for reasons other than DLT will be replaced.

Definition of DLT for the Phase 1 part of this trial:
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/mm^3 with a temperature of ≥ 38.3 degrees C
    - Grade ≥ 3 thrombocytopenia with clinically significant bleeding requiring medical intervention
    - Grade 4 thrombocytopenia
- Non-hematologic:
    - Grade ≥ 3 toxicities (non-laboratory); excluding:
        - Grade 3 fatigue lasting <7 days
        - Grade 3 fever, chills, rigors and hypotension that is responsive to standard supportive care measures and returns to baseline within 24 hours.
        - 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 3 aspartate aminotransferase (AST) or alanine aminotransferase (ALT) if it represents a 2 grade increase from baseline or if it is accompanied by grade 3 bilirubin elevation

  - Grade 4 aspartate aminotransferase (AST) or alanine aminotransferase (ALT)

- Other (non-AST/ALT) non-hematologic Grade ≥ 3 laboratory value if the abnormality leads to overnight hospitalization

- Grade > 2 toxicities possibly or probably related to study procedures

- Any Grade 3 CRS which does not resolve in 7 days to Grade 0 or 1 and is considered possibly or probably related to treatment

- Any Grade 2 or higher neurotoxicity (related to CRES/ICANS) that does not resolve to Grade 1 within 72 hours

5.1.7 Rules for discontinuation of CMP-001 (TLR9) + INCAGN01949 (OX40)

Patients must be withdrawn from study treatment for the reasons listed below:

- Occurrence of intolerable side effects

- Intercurrent illness which prevents further treatment

- Patient choice

- Patient pregnancy

- Disease progression by RECIST (Version 1.1) if accompanied by medically significant clinical deterioration, in the judgment of the Investigator. Continuation of treatment through suspected pseudo-progression or radiological progression is permitted if in the opinion of the Investigator the subject has not clinically progressed.
- Any alterations in the patient's condition which justifies the discontinuation of treatment in the investigator's opinion

Unless patients withdraw their consent, disease and survival status data as well as details of future anti-cancer treatments will continue to be collected as described in the table of assessments.

If a patient permanently discontinues study drug for reasons other than disease progression, such as toxicity, the state of disease in terms of progression should be

noted at this time point. Ideally, formal imaging should occur at this point to document the state of disease. Alternatively, the previous scan should be used. Where possible, scanning should continue as per normal practice until progression has been reached as per protocol. The date of progression of disease should be recorded in the CRF. Further treatment is at the treating doctor's discretion.

5.1.8 Intended Dose Delays

Intended doses may be delayed for non-toxicity reasons for up to 14 days (for reasons such as scheduling conflicts), but only with documentation and explanation in the CRF after discussion with the study Principal Investigator.

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 investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician.

5.1.9 Acceptable Concomitant Medications

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 30 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered more than 30 days after the last dose of trial treatment should be recorded for SAEs as defined in Section 9.1.3.

5.1.10 Prohibited Concomitant Medications

Patients are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial. Patients who, in the assessment by the investigator, require the use of any of the below mentioned treatments for clinical management should be removed from the trial.

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy
- Chemotherapy

- Investigational agents other than TLR9 + OX40
- Radiation therapy
    - **Note**: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion and with sponsor approval.

Patients may receive other medications (not listed here as prohibited) that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications, which are prohibited in this trial. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

Diet/Activity/Other Considerations

5.1.11 Diet

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

5.1.12 Contraception

CMP-001 and INCAGN01949 may have adverse effects on a fetus in utero. Furthermore, it is unknown whether CMP-001 or INCAGN01949 has transient adverse effects on the composition of sperm.

For this trial, male patients 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).

Female patients will be considered of non-reproductive potential if they are either:

1. Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

2. Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

3. Has a congenital or acquired condition that prevents childbearing.

Female and male patients of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days for male patients and 180 days for female patients after the last dose of study drug by complying with one of the following:

1. Practice abstinence† from heterosexual activity;

OR

2. Use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female patient's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

  †Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the patient's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-

ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for patients participating at sites in this country/region.

Patients should be informed that taking the study medication might involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study patients of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 180 days after the last dose of trial therapy. If there is any question that a patient of childbearing potential will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

5.1.13 Use in Pregnancy

If a patient becomes pregnant while on trial treatment, the patient will immediately be discontinued from all trial treatment and have end of visit procedures performed and will be followed-up throughout the remainder of the pregnancy. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 2 working days to the Sponsor if the outcome is a serious adverse experience (e.g., 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 the Sponsor. If a male patient impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above and in Section 9.1.3.

5.1.14 Use in Nursing Women

It is unknown whether CMP-001 or INCAGN01949 is excreted in human milk. Since many drugs are known to be excreted in breast milk and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding or plan to breast feed during the course of the trial are not eligible for enrollment and breast feeding is not permitted while taking trial treatment.

<u>Patient Withdrawal/Discontinuation Criteria</u>

Patients may withdraw consent at any time for any reason or be discontinued from the trial at the discretion of the investigator should any untoward effect occur. In addition, a patient may be withdrawn by the investigator or the Sponsor if enrollment into the

trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding assessments to be done at an EOT visit at time of discontinuation or withdrawal are provided in Table 5.

A patient must be discontinued from the trial for any of the following reasons:

- The patient withdraws consent.
- Confirmed disease progression
- Unacceptable adverse events
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the patient
- The patient has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The patient is lost to follow-up
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 7.1.5.3 (End of Treatment and Survival Follow-up). After the end of treatment, each patient will be followed for 30 days for adverse event monitoring after the end of treatment as described in Table 5. Patients who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each patient will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

Patient Replacement Strategy

Patients who discontinue from the study will not be replaced. Patients who discontinue treatment without progression will be followed to determine their disease status at 6 months. Patients who are enrolled into the trial, but fail to receive CMP-001 (TLR9) + INCAGN01949 (OX40) may be replaced.

Clinical Criteria fo**r** 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 clinical trials indicates a potential health hazard to patients

6.0 Study Calendar

Table 6. Screening – Treatment Period

	SCREENING	TREATMENT						
STUDY WEEK		1	2	3	4	5	6	8
Scheduling Window (Days):	-28 to -1	± 1	±2 days	±2 days	±2 days	±2 days	±2 days	±1 week
Informed Consent	x [a]							
Inclusion/Exclusion	x	x						
Demographics and Medical History	x [b]							
Prior and Concomitant Medication Review	x	x	x	x	x	x	x	
Review Adverse Events		x	x	x	x	x	x	
Physical Examination [c]	x	x		x	x	x	x	
Vital Signs [d]	x	x	x	x	x	x	x	
ECG	x						x	
ECOG [e](see appendix 2)	x	x	x	x	x	x	x	
CBC with Differential	x	x	x	x	x	x	x	
Comprehensive Serum Chemistry Panel [f]	x	x	x	x	x	x	x	
Urinalysis	x	x	x	x	x	x	x	
Serum β HCG Pregnancy Test (if applicable) [h]	x	x	x	x	x	x	x	
PTT/INR and aPTT	x				x	x	x	
Tumor Imaging [I, J]	x[i]							x
•CA 19-9 (or CA 125, or CEA if not expressers of CA 19-9)[k]	x	x			x		x	
Tumor Biopsy [l]	x				x		x	
Central Blood Samples 3 X 10 mL[m]	x	x			x		x	
Autoimmune lab panel [n]	x							
Thyroid Function Tests	x				x		x	
Hepatitis Testing (HepBsAg, HepBcAb, HCV Ab)	x							
HIV antibody testing	x							
CMP-001 (SC dose is 5mg)		x	x					
CMP-001 (IT dose is 10mg)				x	x	x	x	
INCAGN01949 (IT) in mcg[o]				x	x	x	x	

Table 4 Screening through –Treatment Period

a. Written IRB-approved informed consent must be obtained prior to any screening assessments being performed.

b. Documented medical history to include concurrent baseline conditions (using NCI-CTCAE V5. Appendix 1), prior cancer treatment and surgeries. Any events occurring from consent to first dose of study medication will be recorded as medical history.

c. Complete physical exam including height and weight at screening, directed physical exam for day 1 of Week 1, 3 and 6 (if clinically indicated) and at the EOT, if deemed necessary.

d. Vital signs to include: Blood pressure, pulse, pulse oximetry, respiratory rate, weight, and temperature. Height will be measured at screening only.

e. ECOG Performance Status must be 0 or 1 to be eligible for entry to the study.

f. Refer to Table 8 for details of required labs to be included. Adequate organ function must be demonstrated in accordance with protocol criteria **within 10 days of start of study medication** as defined in Table 2. **The following labs are to be drawn at screening, Week 4, end of treatment only and as clinically indicated: LDH, lipase, amylase, magnesium, phosphorous, uric acid.**

h. Negative serum pregnancy test is required for women of child-bearing potential within 72 hours of start of study medication; adequate contraception (both males and females) as defined by the protocol (refer to Section 5.1.12) should be used throughout the study and for 180 days past the last dose for females and 120 days for males.

i. CT/MRI to document disease status at baseline to include chest abdomen and pelvis and other regions as clinically indicated. A screening CT/MRI is not necessary if the patient's last scan was obtained within 28 days before the screening visit.

j. The same radiographic procedures used to document disease status at baseline must be used throughout the study. Tumor assessments will be conducted using CT or MRI, approximately every 8 weeks (+/- 1 week) until study discontinuation or disease progression, whichever is later. All sites of disease must be followed using the same baseline assessment method. Confirmatory assessment of complete response (CR) or partial response (PR) must be performed no less than 4 weeks after the initial documentation of response.

k. CA19-9 (or other relevant tumor markers) assessments will be taken at baseline and at weeks 4 and 6 during the trial treatment period. All CA19-9 assessments must be assayed by the same laboratory for each patient. The Investigator is encouraged to obtain radiological assessments and tumor marker values earlier if there is a strong clinical suspicion of disease progression, in order to confirm or refute the clinical impression.

l. Baseline biopsy to be obtained during the screening period. If possible, a biopsy will also be collected on day 1 of week 4 and 6.

m. Each patient will have 3 X 10 mL vials of blood collected at the following time points: Pre-treatment (0-14 days prior to Week1/day1), prior to treatment on day 1 of Week 4 and 6.

n. Autoimmune lab panel to be collected at Screening and EOT

o. Reminder INCAGN01949 is dosed in micrograms (mcg) per m^2 and CMP-001 is in milligrams (mg) as a flat dose.

Table 7. End of Treatment –Follow-Up

EOT thru Follow-Up Period	EOT	Every 12 weeks
Scheduling Window (Days)	14-28 ± 2 days of last dose	
Post-study anticancer therapy status		X
Survival Status		X
Tumor imaging[b]		X
Directed Physical Examination [a]	X	
Concomitant Medication Review	X	
Review Adverse Events	X	
Vital Signs	X	
ECG	X	
ECOG (see appendix 2)	X	
Hematology: CBC with Differential	X	
Comprehensive Serum Chemistry Panel	X	
Urinalysis	X	
Tumor Imaging [b]	X	
Autoimmune lab panel	X	
CA19-9 (or Relevant Tumor Marker)[c]	X	
Review contraception use as required by protocol Section 5.1.12 (where applicable) [d]	X	
Contact Information Review[e]	X	

Footnotes for Table 5. End of Treatment-Survival Follow-up

a. Directed physical exam at the EOT, if deemed necessary.

b. The same radiographic procedures used to document disease status at baseline must be used throughout the study. **Tumor assessments will be conducted using CT or MRI, every 8+/- weeks until study discontinuation or disease progression. After the first 12 months on trial, then assessments will be done every 12 +/- 1 weeks**. All sites of disease must be followed using the same baseline assessment method. Confirmatory assessment of complete response (CR) or partial response (PR) must be performed no less than 4 weeks after the initial documentation of response. An EOT CT/MRI is not necessary if the patient's last scan was obtained within 28 days before the EOT visit.

c. All CA19-9 (or other relevant tumor marker) assessments must be assayed by the same laboratory for each patient.

d. Adequate contraception as defined by the protocol should be used throughout the trial and for at least 120 days for males w/WOCBP sexual partner and 180 days for WOCBP from the last dose of trial treatment. Refer to Section 5.1.12 for complete details.

e. Site to confirm contact information for patient and a designated family member and remind patient of FU telephone contact that will be conducted every 12 weeks for survival status.

7.0 TRIAL PROCEDURES

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

7.1 Trial Procedures

The Trial Flow Chart - Section 6 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 for reasons related to patient safety.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential patient prior to participating in a clinical trial.

7.1.1.1.1 General Informed Consent

Consent must be documented by the patient's dated signature. A copy of the signed and dated consent form should be given to the patient before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the patient must receive the IRB's approval/favorable opinion in advance of use. The patient should be informed in a timely manner if new information becomes available that may be relevant to the patient'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 patient's dated signature or by the patient'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 requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 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 patient has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 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 patient within 28 days before starting the trial. Treatment for the disease for which the patient has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the patient during the trial. All medications related to reportable SAEs should be recorded.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

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

7.1.1.5.2 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 patient initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the EOT visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the patient will move into survival follow-up.

7.1.1.6 Assignment of Screening Number

A patient will be assigned a screening number once they provide written informed consented for the study. This screening number will be site specific and maintained on a Screening log in the Investigator Site File.

7.1.1.7 Assignment of Enrollment Number

Eligible patients will be assigned an enrollment number that will serve as the patient's number throughout the trial. This enrollment number will be site specific and maintained on an Enrollment log in the Investigator Site File.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each patient to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0 (Appendix 1). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 9.0 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 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.

7.1.2.3 Directed Physical Exam

For weeks 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.

7.1.2.4 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 6.0). Vital signs should include temperature, pulse, pulse oximetry, respiratory rate, weight and blood pressure. Height will be measured at screening only.

For the first 5 CMP-001 dosing visits (SC W1D1, W2D1 and IT W3D1, W4D1, W5D1) vital signs are to be collected prior to CMP-001 dosing, and at 30 (±15) minute intervals for 4 hours following CMP-001 dosing. 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 (2 SC and 3 IT). Reduced observation periods can be implemented starting with the 6th dose of CMP-001.

Vital signs should be taken in the supine or seated position, following ≥ 3 minutes of rest.

When vital signs are scheduled at the same time as a blood sample, the vital sign measurements may be obtained within 15 minutes before the scheduled blood draw. If an indwelling cannula is being used to obtain plasma samples, blood pressure should be measured in the arm opposite to the cannula placement.

7.1.2.5 Electrocardiogram

A single standard, 12-lead ECG will be obtained at Screening for each subject. ECGs will also be assessed at the 6th (W6D1) dosing visit and EOT.

Assessed ECG parameters will include heart rate and PR, QRS, QT and QT corrected for heart rate (QTc) intervals. QT will be corrected using Fridericia's (QTcF) formula.

Electrocardiograms will be performed after the subject has been resting in supine or semi-supine position for at least 5 minutes.

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.

7.1.2.6 Eastern Cooperative Oncology Group (ECOG) Performance Scale

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

7.1.2.7 Tumor Imaging and Assessment of Disease

Assessment of the patient's pancreatic cancer or other cancer will be evaluated based on tumor assessments using RECIST 1.1 and iRECIST (Section 8).

Tumor assessments for evaluation of response will be conducted using contrast enhanced multiphase (delayed arterial phase and portal venous phase) CT or MRI. Imaging will be obtained every 8 ± 1 weeks until study discontinuation, disease progression.After the end of first 12 months on trial, then assessments will be done every 12 +/- 1 weeks. All sites of disease must be followed using the same baseline assessment method. Confirmatory assessment of complete response (CR) or partial response (PR) must be performed no less than 4 weeks after the initial documentation of response.

All target lesions will be measured by consistent imaging techniques for each patient throughout the study. Suitable imaging techniques include CT-scan, or MRI. The same technique should be used for each evaluation in an individual patient. Copies of the scans must be available for review.

CA 19-9 (or CA 125, or CEA if not expressers of CA 19-9) assessments for patients with pancreatic cancer will be taken at baseline, week 1, 4 and 6 during the trial

treatment period. All CA 19-9 assessments must be assayed by the same laboratory for each patient.

7.1.3 Blood and Tumor Tissue Collection

Each patient will have three 10mL vials (total of 30 ml) of blood collected at the following time points: Pre-treatment (0-14 days prior to week1/day1), and during the trial prior to treatment on W1/D1, W4/D1 and W6/D1. A needle biopsy will be performed at the following time points: pre-treatment (0-14 days prior to week1/day1), and on treatment prior to IT drug administration on W4/D1 and W6/D1.

Tumor and blood samples will be collected pre-treatment and during treatment. These biomarker assessments will potentially aid in understanding the effect of the two agents. All patients will be consented for the collection and use of these samples. All samples will be linked anonymized and only identified by the trial ID and unique sample number allocated by the Sponsor. The results of any exploratory analyses will not be included in the clinical study report and may be reported separately from the main study results.

- The assays described below may be performed with the material derived from each patient (if available). It is likely that not all assays will be performed on samples provided by each patient (possibly because of insufficient tumor material or inadequate sample quality). Outcome measures may include but are not limited to:

- Determine OX40 expression within the lymphocyte subsets (Teff and Treg)

- Flow cytometry performed on pre and post treatment aspirates to quantify T cells and tumor cells

- On tissue samples collected prior to, and during, treatment, we will:

    - Use flow cytometry to enumerate CD4+ and CD8+ T cell subsets, and the expression of activation/differentiation markers (including CD127, HLA-DR, CD45RO, CCR7, CXCR3) on each

    - Use RT-PCR and sequencing to amplify and characterize the TCRa and b sequences of tumor-infiltrating T cells, looking for evidence of oligo-clonal T cell expansion

    - Perform RNAseq to determine different immune cell populations including T cells and macrophages

7.1.4 Laboratory Procedures/Assessments

Safety laboratory tests for hematology, chemistry, urinalyses, and serum or urine pregnancy tests (if applicable) will be performed by the local laboratory at each investigational site at screening, baseline, and throughout the trial treatment period.

Table 8. Laboratory Tests – performed locally

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR)
Platelet count	Alanine aminotransferase (ALT)	Protein	aPTT
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Thyroid Function Studies (thyroid stimulating hormone [TSH], Free T3, Free T4]
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Autoimmune lab panel (anti-dsDNA, ANA, ANCA, RF, and anti-RNP)
Absolute Neutrophil Count	Carbon Dioxide ‡	pH	Serology panel (HIV, Hepatitis)
Absolute Lymphocyte Count	*(CO_2 or bicarbonate)*	WBCs	
	Uric Acid		
	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		
	Vitamin D • 25-Hydroxy D2		

Hematology	Chemistry	Urinalysis	Other
	• 25-Hydroxy D3 • 25-Hydroxy D Total		
	Amylase		
	Lipase		
	Creatinine		
† Perform on women of childbearing potential only. ‡ If considered standard of care in your region.			

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.0 - Trial Procedures.

7.1.5.1 Screening

Screening of potential patients will be performed only after informed consent is obtained and within 28 days prior to first dose of trial medication (unless stated otherwise below). All necessary laboratory values and assessment reports must be available prior to week1/ day 1.

The following will be completed as part of the screening visit:

1. Written informed consent
2. Medical history including concurrent baseline conditions (using NCI CTCAE version 5.0; Appendix 1), prior cancer therapy (including documentation of prior surgery, adjuvant or neoadjuvant chemotherapy and radiotherapy).
3. Complete physical examination including height (cm) and weight (kg).
4. ECOG Performance Status (see Appendix 2)
5. Vital signs (blood pressure, pulse, pulse oximetry, respiratory rate, weight, and temperature).
6. Computed tomography (CT) / magnetic resonance imaging (MRI) scans to document disease status (including chest, abdomen, pelvis, and other regions as clinically indicated. In addition, brain scan is required to exclude brain metastases if clinically indicated only). If a CT scan was performed within 28 days prior to first dose, new scans are not necessary. However, if new scans are to be done, they should be performed within 5 days prior to starting trial medication.
7. Electrocardiogram (ECG)
8. PTT/INR and aPTT
9. Complete blood count (CBC) with differential and platelet count.
10. Comprehensive serum chemistries (refer to Table 6).
11. CA 19-9 (or CA125 or CEA if not expressers of CA19-9) for patients with pancreatic cancer
12. Urinalysis (refer to Table 6)

13. Serum β-HCG pregnancy test for women of child-bearing potential (refer to Section 5.1.12 for more details)

14. Concomitant medication notation (to include all medications taken within 30 days prior to enrollment)

15. Baseline biopsy of the tumor to be injected.

16. Central Blood Samples to be collected at screening and at the time of each treatment. Three 10 mL vials (must be collected within 14 days of Week 1/Day 1)

17. Hepatitis B (using Hep B sAg, Hep B cAb IgG) and Hepatitis C (using HCV Ab and HCV RNA if HCV Ab is positive)

18. Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies)

19. Thyroid function test

20. Autoimmune lab panel

7.1.5.2 Treatment Period

Patients will be treated at weekly (7day) ± 2 day intervals. Patient must begin Week 1/ Day 1 within 28 days of signing the IRB approved informed consent document and after the screening assessments.

Treatment will be administered by qualified and trained site personnel in a hospital, clinic, or other outpatient setting appropriate for chemotherapeutic infusions. Please reference section 7.1.6 for specific guidance on prophylaxis prior to and after CMP-001 dosing.

For subsequent treatments, all assessments must be conducted within 48 hours (except those noted), or if medical or scheduling conditions require a delay.

Screening clinical evaluations and laboratory assessments may be used as the Week 1 /Day 1 evaluations if they are completed within 48 hours of trial treatment administration.

<u>Week 1 Day 1 (except where noted)</u>

- **Week 1 only:** Inclusion/exclusion review
- Directed physical exam

- Vital signs
- Measurement of weight (kg) and BSA calculation prior to dosing (After Week 1, the BSA only needs to be changed if there has been a change > 10% in body weight from Week 1 /Day 1
- ECOG Performance Status (Appendix 2)
- Hematology: CBC with differential and platelet count
- Serum chemistries (refer to Table 6)
- CA19-9 (or CA 125, or CEA if not expressers of CA 19-9) for patients with pancreatic cancer.
- Urinalysis
- Serum β-HCG pregnancy test. Results must be reviewed prior to treatment initiation confirming a negative serum β-HCG for women of child-bearing potential and documentation of the patient's confirmation of preferred acceptable method of contraception starting from the day of trial treatment initiation or 14 days prior to the initiation of trial medication for oral contraception (refer to Section 5.1.12 for more details).
- As a precaution and as per protocol, patients must be observed on site for at least 4 hours after injection, or until the investigator deems necessary, e.g., until any suspected symptoms have spontaneously disappeared or have been successfully treated.
- Central Blood Sample, 3 X10 mL vials – collected prior to treatment.
- AEs using the NCI CTCAE 5.0 (Appendix 1)
- Concomitant medication notation
- CMP-001 administration (SC administration)

Week 2 Day 1

- Vital signs
- Measurement of weight (kg) and BSA calculation prior to dosing (After Week 1, the BSA only needs to be changed if there has been a change > 10% in body weight from Week 1 /Day 1

- Hematology: CBC with differential and platelet count
- Serum chemistries (refer to Table 6)
- Urinalysis
- As a precaution and as per protocol, patients must be observed on site for at least 4 hours after injection, or until the investigator deems necessary, e.g., until any suspected symptoms have spontaneously disappeared or have been successfully treated. After week 5 this can be reduced based on investigator judgment.
- AEs using the NCI CTCAE 5.0 (Appendix 1)
- Concomitant medication notation
- CMP-001 administration (SC administration)

Week 3 and 5, Day 1

- Vital signs
- Measurement of weight (kg) and BSA calculation prior to dosing (After Week 1, the BSA only needs to be changed if there has been a change > 10% in body weight from Week 1 /Day 1
- Hematology: CBC with differential and platelet count
- Serum chemistries (refer to Table 6)
- Urinalysis
- As a precaution and as per protocol, patients must be observed on site for at least 4 hours after injection, or until the investigator deems necessary, e.g., until any suspected symptoms have spontaneously disappeared or have been successfully treated. After week 5 this can be reduced based on investigator judgment.
- AEs using the NCI CTCAE 5.0 (Appendix 1)
- Concomitant medication notation
- CMP-001 administration (IT administration)
- INCAGN01949 administration (IT administration)

Week 4 and 6, Day 1

- Directed physical exam
- Vital signs
- Week 6 only – Computed tomography (CT) / magnetic resonance imaging (MRI) to document disease status (including chest, abdomen, pelvis, and other regions as clinically indicated. In addition, brain scan is required to exclude brain metastases if clinically indicated only).
- Measurement of weight (kg) and BSA calculation prior to dosing (After Week 1, the BSA only needs to be changed if there has been a change > 10% in body weight from Week 1 /Day 1
- ECOG Performance Status (Appendix 2)
- Hematology: CBC with differential and platelet count
- Serum chemistries (refer to Table 6)
- PTT/INR and aPTT
- CA19-9 (or CA 125, or CEA if not expressers of CA 19-9) for pancreatic cancer.
- Urinalysis
- Needle biopsy of the injected tumor prior to first intratumor injection
- Serum β-HCG pregnancy test. Results must be reviewed prior to treatment initiation confirming a negative serum β-HCG for women of child-bearing potential and documentation of the patient's confirmation of preferred acceptable method of contraception starting from the day of trial treatment initiation or 14 days prior to the initiation of trial medication for oral contraception (refer to Section 5.1.12 for more details).
- As a precaution and as per protocol, patients must be observed on site for at least 4 hours after injection (during week 6 observation time can be reduced), or until the investigator deems necessary, e.g., until any suspected symptoms have spontaneously disappeared or have been successfully treated.
- Central Blood Sample, 3 X10 mL vials – collected prior to treatment.
- AEs using the NCI CTCAE 5.0 (Appendix 1)

- Concomitant medication notation
- Thyroid function tests
- CMP-001 administration (IT administration)
- INCAGN01949 administration (IT administration)
- CT/MRI scan in Week 8 to evaluate disease status (using same imaging method as Baseline).
    - Every 8 ± 1 week until disease progression or study discontinuation (whichever is later), or end of first 12 months on trial, then every 12 +/- 1 weeks, whichever comes first

Note: In order to more precisely determine time to progression, the investigator is encouraged to obtain radiological assessments and CA19-9 values earlier if there is a strong clinical suspicion of disease progression. In order to either confirm or refute the clinical impression.

7.1.5.3 End of Treatment (EOT)

The patient will continue on study treatment until there is evidence of clear-cut tumor progression, has treatment ending toxicities, withdraws from treatment (refer to section 5.1.14) or finishes 6 weeks (6 doses). The following assessments will be performed 14-28 (+/- 2) days after completing the last dose of trial medication or before the initiation of a new anti-cancer treatment, whichever comes first:

- Directed physical exam, if deemed necessary
- ECOG Performance Status (see Appendix 2)
- Vital signs
- ECG
- Hematology: CBC with differential and platelet count
- Serum chemistries
- CA 19-9 (or CA125 or CEA if not expressers of CA19-9) for pancreatic cancer
- Serum β-HCG pregnancy test.
- Review contraception use as required by protocol Section 5.1.12 (where applicable)

- Urinalysis
- Concomitant medications
- CT/MRI scan to evaluate disease status (using same imaging method as Baseline. An EOT CT/MRI is not necessary if the patient's last scan was obtained within 28 days before the EOT visit
- Autoimmune lab panel
- AEs using the NCI CTCAE Version 5.0 (see Appendix 1)

  Patients 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-neoplastic therapy, whichever occurs first. SAEs that occur within 30 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

- Confirm contact information for patient and a designated family member and remind patient of FU telephone contact that will be conducted every 12 weeks for survival status

7.1.5.4 Survival Follow-up

Once a patient experiences confirmed disease progression or starts a new anti-cancer therapy, the patient moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.6 Required Prophylaxis Prior to and After CMP-001 Dosing

CMP-001 has been administered as an IT or SC injection. Intratumoral injection of CMP-001 provides the most direct approach to activate tumor-associated pDC, and thereby may induce a more potent antitumor CD8+ T-cell response.

To reduce the severity of these symptoms associated with CMP-001 treatment, prophylaxis is required. Prophylactic regimens already in place at institutions should

be followed; if not, below is a suggested regimen that has been effective for the treatment of CMP-001 induced AEs:

- Intravenous fluids (eg, approximately 1000 cc IV normal saline)
- Anti-pyretics (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 (ie, 50 to 100 mg hydrocortisone orally every 8 hours) prior to or immediately after injection of CMP-001.

Prophylaxis administration should be completed before initiation of CMP-001 injection. The medications are recommended for oral administration, but IV is acceptable at the discretion of the investigator. It is also highly recommended to continue to administer fluids immediately following the CMP-001 injection, rather than waiting to initiate fluids if hypotension is detected. There is no waiting period between the end of prophylaxis and the start of the CMP-001 injection. The following algorithm (Figure 2) is provided as guidance for the treatment of symptoms associated with CMP-001.

In subjects with hypotension unresponsive to supportive care with intravenous fluids, the administration of stress dose steroids is recommended according to institutional practices. Additional treatment measures may include the use of anti-cytokine therapy per institutional protocol. Prior to dosing an anti-cytokine therapy, it is recommended that blood be obtained to determine the cytokine level believed to be responsible for the AE. The result of the cytokine assay does not need to be available prior to dosing.

For subjects who previously experienced a CMP-001-related Grade 3 or higher AE, prophylaxis with stress dose steroids (50 mg to 100 mg hydrocortisone orally every 8 hours before or immediately after injection of CMP-001 or institutional standard) is recommended for subsequent CMP-001 doses. A minimum dose of corticosteroids of 25 mg prednisone or equivalent (eg, hydrocortisone, methylprednisolone, dexamethasone) is recommended. The selection and dose of corticosteroid should be determined by the Investigator based on clinical parameters.

7.1.7 Subcutaneous Injections with CMP-001

CMP-001 should be injected using aseptic technique. Use of topical and/or local anesthetic is permitted. The injection may be given into any SC site in the body. Please refer to **Appendix 3** for CMP-001 Injection Guideline.

7.1.7.1 Preferred Sites for Subcutaneous Injection

In order to maximize the distribution and exposure to CMP-001, the full volume from a single dose should be distributed to as many SC sites as is practical. It is recommended that equal amounts of drug be injected at each SC site. Please refer to **Appendix 3** for CMP-001 Injection Guideline.

Preferred sites of SC injection include:

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

- Unsuitable sites for injection would include, for example, the palm of the hand or the sole of the foot

7.1.7.2 Method of CMP-001 Subcutaneous (SC) Administration

Using standard aseptic technique, the needle is inserted into the SC tissue. After using gentle backward pressure on the syringe plunger to confirm extravascular location of the needle tip, the desired volume of CMP-001 is injected and the needle is withdrawn. Please refer to **Appendix 3** for CMP-001 Injection Guideline.

7.1.8 Intratumoral Injections with CMP-001 and INCAGN01949

Please refer to **Appendix 3** for CMP-001 Injection Guideline. CMP-001 and INCAGN01949 should be injected into the same lesion. However, the two drugs should not be mixed together since the saline that OX40 is diluted in can interfere with CMP-001. Avoid selecting lesions that may place the subject at undue risk of complications such as lesions near large blood vessels or near the subject's airway. If possible, select a single lesion to be injected throughout the study. Clean the injection site and surrounding area based on standard procedures at your institution.

Biopsy needle should be removed from the body and a fresh injection needle should be used for intratumoral injections. A 25-gauge needle is recommended, however, the choice of needle is at the investigator's discretion. Avoid necrotic or non-solid areas of lesion. Give injections via a fanning motion to maximize distribution throughout the tumor.

Inject CMP-001 and INCAGN01949 via different needles due to saline's ability to destabilize CMP-001. Inject CMP-001 using the first needle. Then withdraw the first needle, and inject INCAGN01949 using the second needle. Do not mix CMP-001 and

INCAGN01949 together. Try to inject both compounds into the same tumor but in different areas.

7.1.9 Observation Period Following CMP-001 and INCAGN01949 Dosing

Following the first 5 doses of CMP-001 and INCAGN01949 patients must be observed for a period of at least four hours for signs and symptoms of reactions to the CMP-001 and INCAGN01949 injections and other AEs. During the 6-week course of treatment patients should be within 20 minutes of the treating clinic.

Based upon the discretion of the Investigator, observation periods can be reduced to one hour for individual patients who demonstrate mild to no AEs post CMP-001 and INCAGN01949 injection for the first 5 doses. Reduced observation periods can be implemented starting with the 6th dose of CMP-001 and INCAGN01949 (W6D1).

8.0 MEASUREMENT OF EFFECT

8.1 Definitions

Evaluable for adverse events

All patients will be evaluable for adverse event evaluation from the time of their first treatment.

8.1.1 Evaluable for response

All patients who have received at least one dose of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of Week 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below.

Response and progression will be evaluated in this study using the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumors) committee as well as the modified iRECIST guidelines. Investigators should note the different requirements for confirmatory scans as well as follow up for the two criteria.

See section 5.1.7 for criteria for continuing treatment past RECIST 1.1 disease progression.

RECIST 1.1 Response and Evaluation Endpoints

8.1.2 Measurable Disease.

Measurable tumor lesions (nodal, subcutaneous, lung parenchyma, solid organ metastases) are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with chest x-ray and as ≥10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥10 mm by CT scan). Malignant lymph nodes must be ≥15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

8.1.3 Non-measurable Disease.

All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

8.1.4 Target Lesions.

When more than one measurable tumor lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Note that pathological nodes must meet the criterion of a short axis of ≥15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

8.1.5 Non-target Lesions.

All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered non-target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as “present” or “absent”.

8.1.6 Response.

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of target and non-target lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures <10 mm (Note: continue to record the measurement even if <10 mm and considered CR). Residual lesions (other than nodes <10 mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases before CR can be accepted. Confirmation of response is only required in non-randomized studies.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non-target lesions must be non-PD. Confirmation of response is only required in non-randomized studies.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥5 mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment or where the tumor burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Table S1: Integration of target, non-target and new lesions into response assessment

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category also Requires
Target lesions ± non target lesions				

CR	CR	No	CR	Normalization of tumor markers, tumor nodes <10 mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	Documented at least once ≥4 wks. from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non target lesions ONLY				
No Target	CR	No	CR	Normalization of tumor markers, tumor nodes <10 mm
No Target	Non-CR/non-PD	No	Non-CR/non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes*	PD	

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

*Investigators should record all new lesions; if the new lesion is felt to be equivocal, treatment may be continued pending further assessments.

8.1.7 iRECIST Response Assessment

Overall response will also be assessed using iRECIST. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression.

Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-point and best overall responses will be recorded separately.

8.1.8 Confirming Progression

Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.

iCPD is confirmed if further increase in tumor burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumor burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions
  - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
  - Continued unequivocal progression in non-target disease with an increase in tumor burden
  - Increase in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST 1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline). As can be seen in table S2, the prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented at the next assessment after iUPD.

8.1.9 New Lesions

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions), and recorded as New Lesions-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case record form.

PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily

unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

Table S2: Time-point (TP) iResponse

Target Lesions*	Non-Target Lesions*	New Lesions*	Time Point Response	
			No prior iUPD**	Prior iUPD**; ***
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD)
iUPD	Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on: o further increase in SOM of at least 5 mm, otherwise remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: o previously identified T lesion iUPD SOM ≥5 mm and / or o NT lesion iUPD (prior assessment - need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: o previously identified T lesion iUPD ≥5 mm and / or o previously identified NT lesion iUPD (need not be unequivocal) and /or o size or number of new lesions previously identified
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on o increase in size or number of new lesions previously identified

* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same. ** in any lesion category. *** previously identified in assessment immediately prior to this TP.

All patients will have their iBOR from the start of study treatment until the end of treatment classified as outlined below.

Table S3: iRECIST Best Overall Response (iBOR)

TPR1	TPR2	TPR3	TPR4	TPR5	iBOR
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iPR, iSD, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	PR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, ICPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD

1. Table assumes a randomized study where confirmation of CR or PR is not required.
2. NE = not evaluable that cycle.
3. Designation “I” for BOR can be used to indicate prior iUPD to aid in data interpretation.
4. For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation.

8.1.10 Response and Stable Disease Duration (RECIST 1.1 and iRECIST)

Response duration will be measured from the time measurement criteria for CR/PR or iCR/iPR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

8.1.11 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the “merged lesion”.

8.1.12 Clinical Lesions.

Clinical lesions will only be considered measurable when they are superficial and ≥10 mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

8.1.13 Chest X-ray.

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

8.1.14 CT, MRI.

CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Other specialized imaging or other techniques may also be appropriate for individual case. For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

8.1.15 Ultrasound.

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

8.1.16 Endoscopy, Laparoscopy.

The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

8.1.17 Tumor Markers.

Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.

8.1.18 Cytology, Histology.

These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

9.0 ASSESSING AND REPORTING ADVERSE EVENTS

9.1 Definition of Adverse Event

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation patient 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 any of the component of trial treatments, is also an adverse event.

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 9.1.3. The investigator will make every attempt to follow all patients with non-serious adverse events for outcome.

9.1.1 Reporting of Pregnancy and Lactation

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

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the patient 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 lactations that occur from the time of treatment allocation/randomization through trial treatment or 30 days following cessation of treatment if the patient 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.

An “Initial Pregnancy Report” or equivalent must be completed in full and emailed to SafetyReporting@Incyte.com or faxed to (+) 1-866-981-2057 and to cfrench@checkmatepharma.com within 24 hours of discovery of a pregnancy of a subject who has taken the Incyte product or the pregnancy of a partner for a subject who has taken the Incyte product. The “Follow-up Pregnancy Report Form” or equivalent must be completed and emailed to SafetyReporting@Incyte.com or faxed to (+) 1-866-981-2057 and to cfrench@checkmatepharma.com within 30 days after delivery, so that Incyte is provided with information regarding the outcome of the pregnancy. If the pregnancy results in any events which meet the serious criteria (i.e., miscarriage or termination), the SAE reporting process needs to be followed and the timelines associated with a SAE should be followed.

9.1.2 Immediate Reporting of Adverse Events to the Sponsor

In addition, all SAEs must be reported promptly to Checkmate Pharmaceuticals (SafetyInbox@checkmatepharma.com and cfrench@checkmatepharma.com) after the Investigator recognizes/classifies the event as a SAE. The specific reporting time frame depends on the type of SAE. For life-threatening or fatal events, the Investigator must report initial information on the SAE within 24 hours/1 business day of becoming aware of the event, preferably by fax or alternatively by phone or email; at a minimum, a description of the event and the Investigator’s judgment of causality must be provided at the time of the initial report. Attribution of adverse events specifically to either CMP-001 or INCAGN01949 may be challenging, but every effort should be made to assign

attribution to the individual drug rather than the combination of the two drugs. If an SAE is reported by phone or by e-mail, the Investigator must fax a completed SAE report form to TBD within 1 business days. The Investigator should follow all AEs/SAEs observed during the study until they resolve or stabilize, the patient is lost to follow-up, or the events are otherwise explained. TBD is responsible for notifying the relevant regulatory authorities and study partners of certain Serious Adverse Events.

The Principal Investigator (PI) must report all Serious Adverse Events (SAEs) to Incyte within 24 hours of learning of an event, regardless of the PI's causality assessment. This notification should be provided on a completed Serious Adverse Event (SAE) form. SAE reporting for each subject begins the day the informed consent is signed by the patient and within 30 days after subject has completed or discontinued from the study or has taken last dose of the study drug, or as described in the protocol.

SAEs, occurring using Incyte study drug, are reported in accordance with the effective protocol. SAEs occurring with any other commercial drug are reported to the manufacturer of that drug in accordance with regulations and protocol.

Initial SAEs and/or subsequent follow-up reports should be reported via email to SafetyReporting@Incyte.com or fax (+) 1-866-981-2057 and cfrench@checkmatepharma.com. SAE reports should be for a single subject. SAE forms should be sent with a cover sheet and any additional attachments.

All adverse event information is reported to Incyte on the Principal Investigator's/Institution's Adverse Event Report Form, or a CIOMS-I or MedWatch Form FDA 3500A, or on an Adverse Event Report Form which may be provided by Incyte upon request. The Principal Investigator does not provide medical records (e.g., discharge summary) to Incyte, unless specifically requested.

9.1.3 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose that:

- Results in death (In this study, deaths that are unequivocally due to Disease Progression are not to be reported as SAEs);
- 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

For the time period beginning when the consent form is signed until treatment initiation any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any patient must be reported within 24 hours to the Sponsor and within 2 working days if it causes the patient 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, or a procedure.

For the time period beginning at treatment initiation through 30 days following cessation of treatment, or until the patient 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 other than progression of the cancer under study whether or not related to the trial treatment, must be reported within 24 hours to the Sponsor.

Additionally, any serious adverse event, considered by an investigator to be related to trial treatment 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 the Sponsor.

The USC NCCC Data and Safety Monitoring Committee (DSMC) must be notified within 24 hours of submission of such reportable event to the IRB. The patient ID and the study number as well as identifier of the SAE report should be submitted to the DSMC Coordinator via email or Fax to the attention of the DSMC Coordinator at 323-865-0089.

The FDA should be notified within 7 business days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and 15 business days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

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

9.1.4 Evaluating Adverse Events

An investigator will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP website at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

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.

Disease Progression is not considered an AE in this study

When flu-like or cytokine release-like symptoms are reported, each individual symptom should be recorded as a separate AE in the Electronic Data Capture system.

When specific adverse events are not listed in the CTCAE they will be graded by the investigator according to the following grades and definitions, consistent with the CTCAE Version 5.0.

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

- Grade 4: Life-threatening consequences; urgent intervention indicated.

- Grade 5: Death related to AE.

Duration

The investigator will record the start and stop dates of the adverse event. If less than1 day, this will be indicated in the appropriate length of time in units.

Action Taken

Did the adverse event cause the trial treatment to be discontinued?

Relationship

All adverse events regardless of CTCAE grade must be evaluated for relationship to each individual drug.

The determination of the likelihood that trial treatment caused the adverse event will be provided by an investigator. 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 trial treatment and the adverse event based upon the available information.

The following components are to be used to assess the relationship between trial treatment and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the trial treatment caused the adverse event (AE):

Exposure: Is there evidence that the patient was actually exposed to trial treatment 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 trial treatment? Is the time of onset of the AE compatible with a drug-induced effect?

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?

Dechallenge: Was trial treatment 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 trial treatment; or (3) the trial is a single-dose drug trial); or (4) trial treatment is/are only used one time.

Rechallenge: Was the patient re-exposed to trial treatment 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: If a rechallenge is planned for an adverse event which was serious and which may have been caused by either of the trial treatments, or if reexposure to trial treatment poses additional potential significant risk to the patient, 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 trial treatment or drug class pharmacology or toxicology?**

Relationship	**Attribution**	**Description**
Unrelated to the trial treatment/intervention	Unrelated	The AE is clearly NOT related to the trial treatment/intervention

	Unlikely	The AE is *doubtfully related* to the trial treatment/intervention
Related to the trial treatment/intervention	Possible	The AE *may be related* to trial treatment/intervention
	Definite	The AE *is clearly related* to trial treatment/intervention

9.1.5 Sponsor Responsibility for Reporting Adverse Events

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

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design

This is a phase 1B/II pilot trial. Up to 21 patients will be enrolled in Phase IB, and up to 21 patients in Phase II. Eligible patients will be treated with CMP-001 + INCAGN01949. The dose of CMP-001 + INCAGN01949 used in the Phase II study will be determined from the safety responses occurring in the Phase 1B dose study.

Trial treatment will be administered per the schedule as described in 6.0. The primary endpoint will be response rate, objective response rate (CR+ PR), as well as disease control rate (CR+ PR+ SD x 16 weeks).

The secondary endpoint will be incidence of toxicities, percent of patients who normalized their CA19-9, progression free survival, and overall survival.

10.2 Sample Size Considerations

The sample size (estimated to be between 3 and 21 patients) during dose escalation (Phase IB) cannot be precisely determined and depends on the observed toxicity. The Phase II portion is designed to rule out an ineffective disease control rate of 5% (null hypothesis) versus a hypothesized disease control rate of 30% (alternative hypothesis). In phase II, we will treat an initial cohort of 10 patients, and if no patient demonstrates disease control, defined as a CR, PR, or SD for 16 weeks, the trial will be closed. If there are 1 or more patients with disease control, the trial will be expanded to 21 patients (likely of a specific tumor type).Four or more out of 21 patients with disease control will be sufficient evidence for rejection of the null hypothesis of insufficient activity of the regimen. Enrollment will be suspended after the first stage of the phase II portion to assess for futility. This Simon two-stage minimax design has a power of 90% at a one-sided Type I error rate of 2.5%.

Statistical Analysis Plan

10.3 Analysis of the Conduct of the Study

Enrollment, major protocol violations, and discontinuations for the study will be summarized.

10.4 Analysis of Patient Characteristics

Demographic and baseline characteristics, such as age, race, BSA, duration of pancreatic or other cancer, site(s) of metastatic disease, prior cancer treatment, and baseline ECOG performance status will be summarized using means (± standard error) or medians (range) for continuous variables and proportions for categorical variables.

10.5 Analysis of Trial Treatment Administration

Trial treatment (CMP-001 + INCAGN01949) administration will be listed and dose modifications will be flagged. Mean and standard deviations will be used to summarize the average dose received.

10.6 Analysis of Toxicities

Incidence of toxicity will be assessed through summaries of adverse events, clinically relevant changes in laboratory results, and vital signs. All patients who receive any amount of trial treatment will be included in the analysis.

All adverse events occurring on or after Week 1/day 1 will be summarized by body systems and per grade according to NCI-CTC Version 5. Additionally, all serious adverse events as defined in section 9.1.2.1 will be listed separately and tabulated.

10.7 Analysis of Primary Endpoint

The objective response for each patient (complete response, partial response or stabilization of disease) will be assessed at the determined evaluation time points as detailed in 6.0. The duration of objective response as determined by the investigator and the time to disease progression and duration of survival will be assessed for each patient.

Progression-free survival is defined as the interval from the date of registration (i.e. assignment of patient number) to the earliest date of documented evidence of recurrent or progressive disease, or the date of death due to any cause, whichever occurs first. Patients who do not progress and remain alive will be censored at their last radiographic assessment date. Overall survival will be measured from the date of registration (i.e. assignment of patient number) to the date of death due to any cause, or the date of last contact (censored observations).

The efficacy analysis will include summaries for the following parameters: complete response rate (CR), objective response rate (CR + PR), disease control rate (CR + PR +

SD at 16 weeks), percent of patients who normalize their CA 19-9 (or CA 125 or CEA if these are used to follow the patient disease), progression-free survival (PFS), and overall survival (OS). The efficacy analysis will only be conducted on patients who have received at least one dose of CMP-001 and INCAGN01949 and have at least one post baseline tumor assessment. All proportions will be estimated using an exact 95% binomial confidence interval. For the estimation of progression-free and overall survival, a Kaplan-Meier analysis will be performed.

11.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

11.1 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.

The study pharmacist at each participating site will be responsible for maintaining a record of shipment, receipt and dispensation of study medication(s). The study pharmacist will utilize an NCI drug accountability template for documenting dates, and amounts/doses received from the sponsor and dates, patient initials and doses dispensed to the patient.

The study Research Coordinator(s) and Data Manager(s) will be responsible for drug accountability of dispensed and returned drug in accordance with the USC CISO SOP.

For the purpose of this trial the term *investigational products* refer to both TLR9 agonist (CMP-001) and OX40 (INCAGN01949).

CMP-001 (TLR9) will be provided by CHECKMATE PHARMACEUTICALS 45 Main Street, 2nd Floor Cambridge, MA, 02142

INCAGN01949 (OX40) will be provided by Incyte Corporation 1801 Augustine Cut-off Wilmington, DE 19803

11.2 Packaging and Labeling Information

11.2.1 CMP-001

CMP-001 drug product is supplied as a 5.0 mg/mL concentration and is described as follows:

- CMP-001 5.0 mg/mL is a colorless to pale yellow/brown opalescent liquid practically free of particles. Each single use vial contains 1.0 mL of CMP-001 (extractable volume of 1.0mL=5.0mg) with a 0.1 mL overfill.

The CMP-001 study drug vials and kit cartons will be labeled with the following information:

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

11.3 Storage and Handling Requirements

11.3.1 CMP-001

All CMP-001 will be transported, received, stored, and handled in accordance with the container or drug product kit/product label, the instructions supplied to the site and its designated pharmacy personnel, the site's standard operating procedures (SOPs), and applicable regulations.

Appropriate storage and transportation conditions will be maintained for the drug product vials from the point of manufacture up to delivery of each drug product. All shipments of drug product vials will include a temperature monitoring device that records required storage conditions for the vials, at regular intervals for the entire time the shipment is in transit.

Upon receipt by the site, the designated site personnel will examine the shipment and temperature monitoring devices to verify the drug product vials were received in acceptable condition. If not received in acceptable condition, the site must notify the CRA and the site should quarantine the drug until a decision has been made by Checkmate. Once inspected, CMP-001 vials should be stored at the specified temperature (2°C to 8°C) in a locked area accessible only to designated site personnel until dispensing. Once

dispensed, drug product vials will be stored in a limited access area under appropriate environmental conditions.

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

All original vials, whether empty or containing CMP-001 will be kept at the site. Used vials will not be dispensed again (even to the same subject) nor will they be relabeled or reassigned for use by other subjects. Contents of the drug product vials will not be combined. Unused vials will be available for verification by the study monitor.

At the termination of the study, a final drug accountability review and reconciliation must be completed, and any discrepancies must be investigated and their resolution documented.

All drug product vials will be destroyed onsite as per institutional SOPs, after site close out has been completed.

11.3.2 INCAGN01949

11.3.2.1 Description and Administration

The study drug (INCAGN01949) is in liquid form in the formulation buffer of 20 mM histidine, 250 mM sorbitol, pH 6.5 to be used for IT infusion.

Study drug will be diluted in acceptable admixture as outlined in the Pharmacy Manual and will be administered by qualified personnel as an IT injection on Day 1 of Weeks 3, 4, 5, and 6. The Pharmacy Manual contains additional information and instructions for study drug preparation and injection. **Do not mix INCAGN01949 with CMP-001 as saline destabilizes this drug.**

11.3.2.2 Supply, Packaging, and Labeling

Study drug will be supplied as 5 mL of aqueous solution in 10 mL glass vials with 10 mg/mL of INCAGN01949. Study drug will be packaged as open-labeled supplies, and each vial will be labeled and placed in a carton. The Pharmacy Manual contains additional information regarding supply, packaging, and labeling of study drug.

The investigator will take responsibility for and take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study drug in accordance with the Protocol and any applicable laws and regulations.
All Incyte investigational product labels will be in the local language and will comply with the legal requirements of each country.

11.3.2.3 Storage

Study drug must be stored refrigerated (2°C-8°C) and protected from light in a secure, limited access location. Receipt and dispensing of study drug must be recorded by an authorized person at the study site. Study drug may not be used for any purpose other than that stated in the Protocol. The Pharmacy Manual contains additional information regarding storage of study drug.

12.0 ADMINISTRATIVE AND REGULATORY DETAILS

12.1 Institutional Review Board/Ethics Committee Approval and Consent Process

Before trial initiation, this protocol and informed consent form will be submitted for review and approval to the IRBs charged with oversight for the clinical sites. In addition, any form of proposed advertising and advertising text for patient recruitment must be reviewed and approved by the Sponsor prior to submission to the IRB. The Investigator will forward to the Sponsor or their nominated designee a copy of the IRB's approval of this protocol, any amendments, informed consent form, and any modifications to the informed consent, based on the FDA regulations set forth in 21 CRF 56 of the *Code of Federal Regulations,* as well as those of the applicable regulatory bodies in all other participating countries outside of the U.S.

In addition, the Investigator will be responsible for forwarding to the Sponsor or their nominated designee a description of the IRB members (including profession and affiliation) or a United States (US) Department of Health and Human Services (DHHS) General Assurance number and expiration date. If neither of these is available, the chairperson must submit a statement indicating that the members of the board responsible for the review meet the FDA and other appropriate regulatory requirements. In addition, the labeling for all approved trial medications should be submitted to the IRB for information purposes.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing a dated IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person authorized to obtain the informed consent.

12.2 Investigators Protocol Agreement and Required Documentation

The Investigator must sign the Investigator's Protocol Agreement. The original must be kept on file at the Sponsor and the Investigator must retain a copy. The completed Investigator's Protocol Agreement signifies agreement to comply with all procedures outlined by this protocol by the Investigator. An Investigator's Protocol Agreement must be signed if and when a protocol amendment is issued by the Sponsor.

Before the study can be initiated at any site, the following documentation must be provided to the USC Clinical Investigation Support Office (CISO):

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Protocol signature page with Investigator signature
- Form FDA 1572 appropriately filled out and signed with appropriate documentation
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

12.3 Investigator Obligations

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

12.4 Registration Procedures

Multi-Site Registration:
All sites must register all patients with the Café USC database before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the CISO Quality Assurance Manager. To register a patient, fax the Protocol Eligibility Form, signed IRB approved ICF

and HIPPA to 323-865-0089 Monday through Friday, 8:00AM-4:00PM PST. At the same time, notify the QA Manager of pending registration by calling 323-865-0451 or 323-865-0420.

After the eligibility is confirmed by the QA manager, site Research coordinator or DM will register the patient into USC Norris Cancer Center database "café", by accessing the Registration forms. Likewise, after the patient has completed the study, the Off Study forms in cafe will need to be completed, for Off Treatment and Off Study.

USC Registration:
For patients enrolled at USC, the Research Coordinator must complete the protocol eligibility form to ensure that the patient is eligible. The PI will review the patient eligibility (with assistance from the Research Coordinator- who will assemble the required source documents and do an initial review) prior to registering the patient on study.

The Research Coordinator or data manager will then register the patient into the Cancer Center database, Café, by accessing the Registration forms. Likewise, after the patient has completed the study, the Off Study forms in Cafe will need to be completed, for Off Treatment and Off Study.

12.5 Slot Assignment

The availability of slots and the assignment of patients to a specific dose level in a specific cohort will be done by the phase I committee in the USC Norris Comprehensive Cancer Center.

12.6 Confidentiality

The Investigator and any other personnel involved in this trial shall not disclose, or use for any purposes (other than for the performance of this trial any data, records, or other information (hereinafter collectively "information") disclosed to the Investigator or other trial personnel. Such information shall remain the confidential and proprietary property of the Sponsor and shall be disclosed only to the Investigator or other designated trial personnel.

Patient confidentiality will be ensured by using assigned site-specific Screening and numbers (refer to Section 7.1.1.6) throughout the trial.

The original data collection forms will be kept in secure file cabinets. For USC patients, forms will be kept in the Clinical Investigations Support Office (CISO).

12.7 Compliance with Financial Disclosure Requirements

All Investigators will be required to submit written financial disclosure to the Sponsor prior to participating in this clinical trial and any changes in disclosures during the course of the trial as per 21 CFR part 54.

All investigators will follow the University conflict of interest policy. Any USC investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must complete a "Statement of Outside Interests Related to Research" Form. The application is reviewed and approved by the Conflict of Interest Review Committee (CIRC) USC conflict of interest policy is available at http://ooc.usc.edu/conflict-interest-research.

12.7.1 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are patient to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow patients to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

12.8 Quality Management System

All aspects of the study will be carefully monitored by the and/or its authorized representative for compliance with applicable government regulations with respect to current ICH GCP guidelines as well as other applicable regulations and guidelines.

12.9 Data Monitoring Plan

The Data Safety Monitoring Committee is an independent body responsible for the safety of study subjects through the review of new protocols to ensure an adequate adverse event assessment/reporting plan, study stopping rules and through the real-time and periodic monitoring of severe adverse events (SAEs) or those AEs that require expedited reporting. The DSMC performs quarterly and annual safety reviews as well as interim efficacy/futility analyses on institutional trials. DSMC procedures are detailed in USC NCCC DSM Plan available on the CISO website.

12.10 Data Management

12.10.1 Case Report Forms

All the clinical data will be captured by the site on electronic case report forms (eCRFs). The eCRFs will be used for all consented patients. The investigator and trained trial personnel will enter and edit the data via a secure network, with secure identification and password requirement. A complete electronic audit trial will be maintained. The investigator will be required to provide approval of all data to confirm accuracy. Copies of the eCRFs will be provided to the investigator at the conclusion of the trial.

12.10.2 Patient Consent Form

At the time of registration, signed and dated copies of the patient Informed Consent with the Human Rights and the HIPAA authorization must be given to the patient. Institutional policy regarding distribution and location of original consent documents should be followed. When a study is opened at two or more institutions, a copy of the signed consent and HIPAA should be sent to USC CISO QA team as soon as possible, and not later than within 5 business days of obtaining consent. For patients consented at USC/LAC, institutional policy should be followed: a copy of ICF and HIPAA should be uploaded to the USC CRO and CISO QA Team. The original will be kept in the patient research chart maintained by the study assigned Data Manager.

12.10.3 Registration Eligibility Worksheet

At the time of registration, the completed Eligibility Worksheet will be submitted to the QA Monitor at CISO for review of eligibility compliance.

12.10.4 Data Collection Forms and Submission Schedule

Protocol data will be entered into eCRFs in iMedidata Rave.

Within two weeks of registration, the data manager will complete the initial set of On Study forms and baseline toxicities.

Within two weeks of completion of each course of treatment, the data manager must complete the Course Assessment, Toxicities, and if appropriate Response data.

After Off Treatment, within two weeks of each follow up, complete the Follow Up forms.

12.10.5 Source Documents

Source documents serve as the evidence of the existence of the patient and the data collected for this trial. Source documents will be the responsibility of the Investigator and will be filed at the site and available as needed by the sponsor or assigned clinical monitor.

Data captured on the eCRF is to be transcribed from source document and must be consistent with any discrepancies explained and documented.

12.11 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

12.12 Data Management and Monitoring/Auditing

Adherence to Protocol/Per Patient: It is the responsibility of the USC Principal Investigator (PI) to ensure that patient recruitment and enrollment, treatment, follow-up for toxicities and response, and documentation and reporting at USC are all performed as specified in the protocol. When a study is opened at two or more institutions, the PI at each institution will assume the responsibilities for the day-to-day monitoring of the trial, as described below.

Day-to-Day Monitoring – Eligibility: At USC, the Study Coordinator will assist the Investigator in reviewing eligibility and will assemble the required source documents, and do a final review by completing an Eligibility Registration Worksheet. When a study is opened at two or more institutions, the PI at each institution will review the patient eligibility in accordance with that institution's policy. For all institutions, the Eligibility Registration Worksheet with a copy of Informed Consent and supporting source documents will be submitted to CISO QA via email or Fax for verification prior to registering the patient on study.

Day-to-Day Monitoring – Informed Consent: Prior to registering the patient on study, the Study Coordinator will review the informed consent, to ensure that the patient has signed and dated the most current IRB-approved form, and that the form has been signed and dated by the person obtaining the consent as well as appropriate witnesses. A copy of the ICF will also be provided to CISO QA for review. CISO SOP 3.3 will be followed.

Day-to-Day Monitoring – Treatment: The PI and co-investigators are responsible for ensuring that treatment is given per protocol. The Study Coordinator will review the treatment orders with the treating investigator. Regardless of who the treating physician is, there will be only one responsible Study Coordinator for each study at each of the hospitals affiliated with the USC Norris Cancer Center. The treating investigator will review the status of each patient on-study, with the Study Coordinator and treating physicians, on an on-going basis. When a study is opened at two or more institutions, CISO QA will periodically audit medical records for the subjects on study at other institutions to ensure compliance and adherence to the protocol.

Data Management – Patient Charts: When a study is opened at two or more institutions, the policy in place at each institution will be followed for maintaining medical and research related records. Such policies will be provided to the CISO QA prior to enrolling 1st patient.

At USC, all written source documents not associated with the study research are maintained in the patient chart, which is stored in the Department of Medical Records at the appropriate hospital. At the Norris Hospital, the official medical record is Cerner. Radiographical images are stored in the Department of Radiology and in an electronic system called Synapse. At Los Angeles County General Hospital the official medical record is called Power Chart. These are the permanent, official documents for each patient on-study. A copy of the signed informed consent, physician's notes, orders, test results and pathology notes are maintained in the patients' hospital charts. It is the responsibility of the research staff to ensure that the patient chart contains the required documents and work closely with treating investigators to ensure all protocol-related assessments are carefully documented. At Hoag, the official medical record is called Epic.

Data Management – Research Charts: When a study is opened at two or more institutions, the policy in place at each institution will be followed for maintaining medical and research related records. Such policies will be provided to the CISO QA prior to enrolling 1st patient. At USC, to facilitate adherence to the protocol schedule and data management, research charts are created to collect copies of the relevant notes, orders and results, that are in the Patient Chart. In Addition, all source documents related to the research, such as original informed consent forms, HIPAA Forms, AE assessment worksheets, disease response worksheets and NTFs are maintained in the Research Charts. Protocol calendars, worksheets, and checklists, are also kept in the research chart. These are maintained in the Clinical Investigation Support Office until the study is completed and the results are published and no further need is anticipated. These are then stored off-site. It is the responsibility of the Data Manager to ensure that the research chart contains all the required documents.

Data Management – Case Report Forms: It is the responsibility of the Data Manager to complete the required case report forms. For in-house trials, case report forms are developed for each trial; these are used to finalize the data entry screens in the Cancer Center clinical trials database. It is the responsibility of the PI to review the Off-Study Summary form which summarizes pertinent toxicity, response and adherence information, once the patient has completed treatment.

12.13 Quality Assurance Monitoring Committee (QAMC) Oversight

The Quality Assurance and Monitoring Committee (QAMC) of the NCCC has the responsibility for study auditing and monitoring for protocol compliance, data accuracy, performance of audits and monitoring of accrual. QAMC procedures are detailed in the NCCC Data Safety and Monitoring Plan available on CISO Website.

QAMC Annual Patient Audits

The QAMC is responsible for conducting audits and providing the initial review of the audits, for all open institutional (i.e. USC initiated), CCCP-sponsored trials, and any trials identified by the CIC. These trials are audited by the QAMC once a year. Faculty and staff at the Cancer Center involved in clinical research – but not directly involved in the research under evaluation – are asked to serve as auditors. Twenty percent of patients accrued during the past 12 months – and a minimum of 2 patients – are selected at

random; however, additional patients may be selected for audit if there is some indication that there might have been a problem or unusual circumstance (possibly related to compliance, toxicity, response or some indication of an irregularity). The audit involves a review of the research chart, hospital medical record (i.e., source documentation) and evaluates the following: documentation of eligibility (including failure to obtain appropriate informed consent) and baseline status of the patient; documentation of adherence to protocol-specified treatment and follow-up; evaluation of toxicity; and evaluation of response or other outcome. In addition, for investigative agents, a drug audit is also performed for these patients by the Research Pharmacist. In addition, for Institutional, Investigator Initiated Trials, Data in the CAFÉ database are compared to the information in the medical record.

QAMC Annual Protocol Review

All open trials are reviewed at least once a year by the QAMC (or more often if stipulated by the CIC). This annual review includes the following: evaluation of the current accrual relative to the planned total accrual; examination of gender and minority accrual; examination of all reported violations; review of past audits and correspondence with the PI; review of results of current audit (by an outside agency or by the NCCC QAMC); review of previous correspondence between the PI and the QAMC/DSMC. The QAMC review process is detailed in USC NCCC DSM Plan available on the CISO website.

12.14 Phase I Committee Oversight

The USC Norris Comprehensive Cancer Center Phase I DLT committee reviews all open institutional phase I studies at regularly scheduled intervals. The committee reviews the adverse events, serious adverse events, and treatment administration for each patient during the DLT observation period as specified per protocol. The committee will determine whether a patient is evaluable for DLT and whether an AE meets the DLT definition or not. Decisions regarding dose escalation, de-escalation and cohort expansion are made by the committee in coordination with the PI.

12.15 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

12.15.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the change.

12.15.2 Non-Emergency Departures from Protocol

A protocol deviation is any variance from an IRB approved protocol.

If the deviation meets all of the following criteria, it is considered a minor protocol deviation that:

- Is generally noted or recognized only after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

If the deviation meets any of the following criteria, it is considered a protocol violation:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious noncompliance with federal regulations, State laws, or University policies.

Protocol Deviations: Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies.

Protocol Violations: All protocol violations will be entered in the clinical trial database by the Research Coordinator. In addition, Research Coordinator and Investigator should report all protocol violations within one (1) week of the knowledge of the event using iStar.

12.15.3 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB as well as to all the sponsoring agencies (FDA, NCI, etc.) for review and for approval prior to implementation. It is the responsibility of the study PI to ensure that the appropriate agencies have been informed of the proposed amendments and that these have been reviewed and approved.

12.16 Data Safety and Monitoring Committee

The Data and Safety Monitoring Committee (DSMC) is an independent body responsible for the safety of study subjects through the review of new protocols to ensure an adequate

adverse event assessment/reporting plan, study stopping rules and through the real-time and periodic monitoring of severe adverse events (SAEs) or those AEs that require expedited reporting. The DSMC performs quarterly and annual safety reviews as well as interim efficacy/futility analyses on institutional trials. DSMC procedures are detailed in USC NCCC DSM Plan available on the CISO website.

An independent DSMC will be formed to evaluate the safety and effectiveness of the study medication for each subject as well as study conduct of each site. The DSMC will also review all SAEs reported by each site. The DSMC will review study data to determine if endpoints are being met and if the study can continue with or without changes to the protocol or if the study should be terminated immediately due to safety concerns or lack of data to support study endpoints. Findings and recommendations of the DSMC will be reported to the Sponsor after each meeting. The DSMC will meet at least once annually and more frequently as needed if safety concerns are raised. Furthermore, prior to opening the Phase II portion of the study a review by the DSMC will be conducted. This treatment regimen combines 2 immunotherapeutic agents with known toxicity profiles. Because cancer is a life-threatening disease, treatments that result in Grade 3 and 4 toxicities are considered to have an acceptable risk profile. Data reported to the sponsor will be received by sponsor representatives on a regular basis and not less than once a month. In addition, SAEs will be reported to the sponsor immediately and reviewed as they are received. Any unacceptable toxicities or severe toxicities that occur more frequently than expected will be discussed by the sponsor, the site Principal Investigators and DSMC members who will decide jointly whether the study should be modified, interrupted, or stopped. The statistical group will provide listings of toxicities on a regular basis.

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APPENDICES

Appendix 1 - NCI CTCAE version 5.0

The CTCAE Version 5.0 can be accessed and downloaded from the CTEP website at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

Appendix 2 – ECOG Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	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	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group.*Am J Clin Oncol.* 1982;5:649-655.

Appendix 3 – CMP-001 INJECTION GUIDELINE

Refer to the current Pharmacy Manual for additional information.

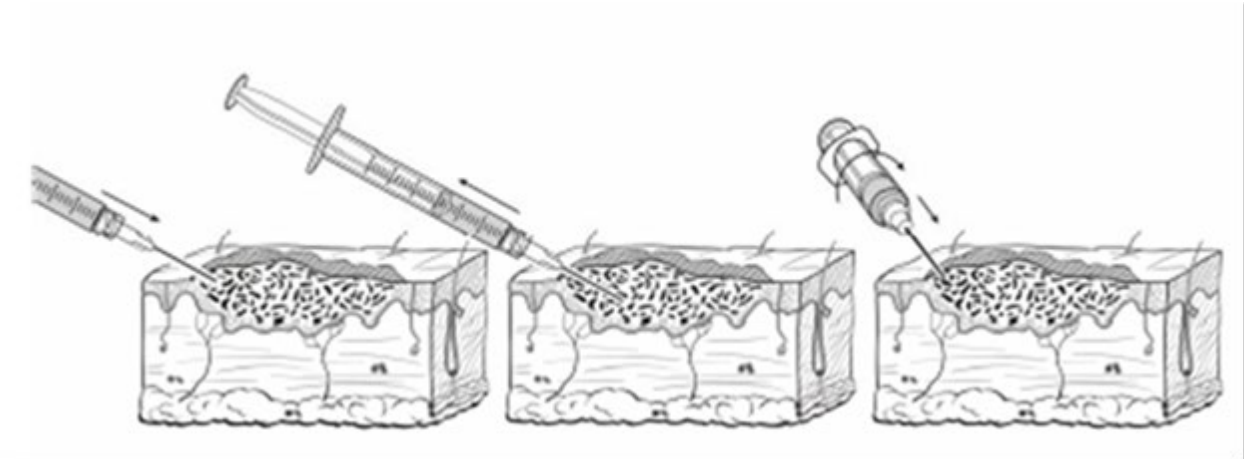
Method of CMP-001 Administration

Intratumoral Injection

Using standard aseptic technique, the needle should be inserted near the tumor periphery (Figure 1 left panel) and advanced into the tumor to the desired depth while maintaining gentle backward pressure on the syringe plunger to confirm an extravascular location of the needle tip. The syringe and needle should be slowly withdrawn to within a few millimeters of the skin or tumor surface while maintaining gentle downward pressure on the plunger to inject the desired volume of CMP-001 along the needle track (Figure 1 middle panel).

With the tip of the needle still under the skin, the syringe should be rotated by ~20^{o} to 40^{o} and the process of insertion and injection during needle withdrawal repeated (Figure 1 right panel). Using this process, CMP-001 is injected IT along multiple tracks through a single insertion point as far as the radial reach of the needle allows within the tumor; 2 insertion points may be used if the tumor is larger than the radial reach of the needle or the intended volume cannot be delivered through a single insertion point. If gentle injection pressure along 5 needle tracks within the tumor has not succeeded in delivering the desired volume, then the remainder of the CMP-001 may be injected peritumorally around the same lesion. If the full volume cannot be injected within the tumor, the remaining drug volume should be injected into a second accessible tumor, if present; otherwise, the remaining volume should be injected SC near an original tumor (peritumoral).

Figure 1: Method for CMP-001 Intratumoral Injection



Recommended Intratumoral Injection Volume Based on Lesion Size

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

Note: If the full 2 mL dose cannot be accommodated within accessible tumor(s), then the remaining volume may be injected peritumorally.

Subcutaneous Injection

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

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

Preferred sites of injection include the following:

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

Figure 2: Preferred Sites of Subcutaneous Injection