PROTOCOL AMENDMENT #4

LCCC 1626: Phase Ib/II Study of IV Nivolumab and Intrapleural Talimogene Laherparepvec for Patients with Malignant Pleural Effusion

AMENDMENT INCORPORATES (check all that apply):

X Editorial, administrative changes
Scientific changes (IRB approval)
X Therapy changes (IRB approval)
X Eligibility Changes (IRB approval)

Amendment Rationale:

This amendment clarifies the requirement that a delay in administration of systemic therapy must be considered clinically acceptable in order for subjects to enroll in the study.
In addition, language was added to clarify that subjects may proceed to systemic treatment in cohort one week following completion of study therapy.

Editorial Change:

1. Minor edits have been made in the document. Placement of hematology footnote number in Time and Events Table corrected.

Therapy Change:

2. The following language has been added to Section 4.1.1, "Cohort Enrollment – Safety Run-In:" "One week following completion of study therapy, subjects may proceed to systemic therapy per their decision with their physician."

Eligibility Change:

1. The inclusion criterion for Dose Level 1 previously stated: "non-pleural disease is not considered a significant risk to the patient OR refractory to standard therapies." That criterion has been modified to state: "Either no systemic therapy available per standard of care, or delay in administration of systemic therapy considered clinically acceptable." See Section 3.1.5.

THE ATTACHED VERSION DATED July 22, 2019 INCORPORATES THE ABOVE REVISIONS

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PROTOCOL AMENDMENT #3

LCCC 1626: Phase Ib/II Study of IV Nivolumab and Intrapleural Talimogene Laherparepvec for Patients with Malignant Pleural Effusion

AMENDMENT INCORPORATES (check all that apply):

X Editorial, administrative changes
Scientific changes (IRB approval)
Therapy changes (IRB approval)
X Eligibility Changes (IRB approval)

Amendment Rationale: As the result of recent FDA approvals making PD-1 frontline therapy in lung and other cancers, this protocol has been amended to remove the requirement for the enrollment of PD-1 naïve subjects.

Editorial, Administrative Changes:

- Updated funding source name, as CareFusion was purchased by Becton Dickinson and Company, and they are the new suppliers of the pleurX catheter
- Editorial and administrative changes throughout the protocol
- Updated Section 7.3.3.8 FDA Reporting to remove extraneous information included in the CRFs and LCCC SOPs
- Removed reporting requirements for the NIH RAC as the NIH RAC is currently no longer regulating gene therapy studies outside of FDA and IBC reviews.
- Updated staff titles in Section 7.4 Data and Safety Monitoring Plan

Eligibility Changes:

- Removed the required for subjects to have received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T lymphocyte associated antigen 4 (CTLA-4) antibody prior to enrollment.

THE ATTACHED VERSION DATED February 5, 2019 INCORPORATES THE ABOVE REVISIONS

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PROTOCOL AMENDMENT #2

LCCC 1626: Phase Ib/II Study of IV Nivolumab and Intrapleural Talimogene Laherparepvec for Patients with Malignant Pleural Effusion

AMENDMENT INCORPORATES (check all that apply):

X Editorial, administrative changes
X Scientific changes (IRB approval)
X Therapy changes (IRB approval)
__ Eligibility Changes (IRB approval)

Amendment Summary

1. Section 1.8.2 Updating Aim, adding whole exome sequencing to RNA sequencing as part of correlative studies. DNA and RNA samples will be extracted from pleural fluid samples.
2. Sections 2.1.2 and 2.4.1.2 corrected to state, Resolution (≤50cc drainage over three consecutive every other day drainages) of pleural fluid accumulation accompanied by patient-defined improvement in symptoms (dyspnea, cough and/or chest pain).
3. Section 2.4.0: viral shedding studies were removed
4. Section 4.1.2: editorial changes explaining standard and study drug drainage.
5. Section 6.1 Time and Event table updated to include Buccal Swab collection at pre-study and C1Day1 if required.
6. Section 6.1, Time and Event table updated with clarification on Chest X-ray and their occurrence as needed and/or after three consecutive drainages of pleural fluids accompanied by patient-defined improvement in symptoms.
7. Footnote for Table 2, #14 updated to include information about collection of pleural fluids at 4 time points, and dividing samples into two portions. Portion one will be used for correlative studies, and the second portion will be distributed to the CTU lab for long-term storage for future studies.
8. Sections 6.3, 6.4.2, 6.4.3, 6.4.4, 6.4.5, 6.4.6, and 6.5.1 updated to include clarification on when chest x-rays will be done
9. Section 8.3, data analysis updated in accordance to changes in Phase II aim.
10. Removed Bristol-Myers Squibb from list of sponsors

THE ATTACHED VERSION DATED June 18, 2018 INCORPORATES THE ABOVE REVISIONS

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PROTOCOL AMENDMENT #1

LCCC 1626: Phase Ib/II Study of IV Nivolumab and Intrapleural Talimogene Laherparepvec for Patients with Malignant Pleural Effusion

AMENDMENT INCORPORATES (check all that apply):

X Editorial, administrative changes
___ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

Amendment Summary

The protocol is revised to clarify that pleural, blood and urine samples collected prior to talimogene laherparepvec administration and 1 hour, 4 hours and 6 hours after talimogene laherparepvec administration at Cycle 1 Day 1, prior to talimogene laherparepvec administration at Cycle 1 Day 8, Cycle 2 Day 1, Cycle 2 Day 8, Cycle 3 Day 1, Cycle 4 Day 1, and at the treatment discontinuation visit to assess viral shedding will be frozen and stored at -80°C for possible assessment of viral shedding for up to two years after study completion. It was also clarified that at Cycle 1 Day 1, Cycle 2 Day 1, Cycle 4 Day 1, and at the treatment discontinuation visit pleural fluid will be separated by the LCCC Immune Monitoring and Genomics Facility (IMGF) into two portions: one portion will be used for correlative studies, and the second portion will be stored for possible assessment of viral shedding. If insufficient amount of pleural fluid is collected, priority will be given to a sample used for correlative studies. The above mentioned clarifications were made in Sections 2.3.5, 6.4.1, 6.4.2, 6.4.3, 6.4.4, 6.4.5 and 6.5.1.

THE ATTACHED VERSION DATED April 26, 2018 INCORPORATES THE ABOVE REVISIONS

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LCCC 1626: Phase Ib/II Study of IV Nivolumab and Intrapleural Talimogene Laherparepvec for Patients with Malignant Pleural Effusion

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Funding Source: AMGEN, Becton Dickinson & Company

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LCCC 1626: Phase Ib/II Study of IV Nivolumab and Intrapleural Talimogene Laherparepvec for patients with malignant pleural effusion

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Signature Page

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.

Principal Investigator (PI) Name:_____

PI Signature: _____

Date:_____

Version: Amendment #4 Version 1.0
Version date: July 22, 2019

LIST OF ABBREVIATIONS

ACD	Acid-citrate-dextrose
ACTH	Adrenocorticotropic hormone
ADCC	Antibody dependent cellular cytotoxicity
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
β-HCG	Beta-human chorionic gonadotropin
BMS	Bristol-Myers Squibb
BUN	Blood urea nitrogen
C	Celsius
CBC	Complete blood count
CBR	Clinical benefit rate
cc	Cubic centimeter
CCR7-CD45-RA+ or RA-	Chemokine receptor 7-CD45-rheumatoid arthritis positive or negative
CD	Cluster of designation
C1D1	Cycle 1, day 1
CPO	Clinical Protocol Office
CPR	Cardio-pulmonary resuscitation
CR	Complete response
CRP	C-reactive protein
CT	Computer tomography
CTLA-4	Cytotoxic T-lymphocyte-associated protein-4
CYP	Cytochrome P450
CV%	Coefficient of variation percent
dL	Deciliter
DILI	Drug-induce liver injury
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DSMC	Data safety monitoring committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
F	Fahrenheit
FSH	Follicle stimulating hormone
5-FU	5-fluorouracil
GCP	Good clinical practice
GM-CSF	Granulocyte-macrophage colony stimulating factor
HBs-Ag	Hepatitis B surface antigen
HBc	Hepatitis B core
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HLA-DR	Huma leucocyte antigen D related
HNSCC	Head and Neck Squamous Cell Carcinoma
HSV-1	Herpes simplex virus 1
huGM-CSF	Human granulocyte-macrophage colony stimulating factor f
IC50	Concentration associated with 50% inhibition of maximal effect
ICP47 and ICP34.5	Infected cell protein 47 or 34.5
IDS	Investigational drug service
IFNγ	Interferon-gamma

Ig	Immunoglobulin
IHC	Immunohistochemistry
IL-6	Interleukin-6
IMIDs	Immunomodulators
IND	Investigational new drug
INR	International normalized ratio
I-O	Immuno-oncology
IP	Intraperitoneal
IRB	Institutional review board
irRC	Immune-related response criteria
ITIM	Immunoreceptor tyrosine-based inhibition motif
ITSM	Immunoreceptor tyrosine-based switch motif
IV	Intravenous
Kg	Kilograms
LCCC	Lineberger Comprehensive Cancer Center
LD50	Lethal dose
LDH	Lactate dehydrogenase
LFT	Liver function test
mAb	Monoclonal antibody
MBS	Modified Borg scale (of perceived dyspnea)
MEL	Melanoma
mg	Milligram
Min	Minute
µL	Microliter
MPE	Malignant Pleural Effusion
MRI	Magnetic resonance Imaging
mRNA-seq	Messenger ribonucleic acid-sequence
MSI-H	Microsatellite instability-high
MTD	Maximum Tolerated Dose
NCCN	North Carolina Cancer Network
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NIH	National Institutes of Health
nM	Nanomolar
NS	Normal saline
NSCLC	Non-small cell lung cancer
OAT	Organic anion transporter
OATP	Organic anion transporter polypeptide
OHRE	Office of Human Research Ethics
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	Programmed cell death receptor-1
PD-L1 or PD-L2	Programmed cell death receptor ligand-1or -2
PET	Positron Emission Tomography
PFS	Progression free survival
PFU	Plaque-forming unit
Pgp	P-glycoprotein
PHI	Personal health information
PI	Principal investigator
PK	Pharmacokinetic(s)

PO	*Per os* (by mouth)
PR	Partial response
PRC	Protocol Review Committee
PT	Prothrombin time
PTT	Partial thromboplastin time
QD	*Quaque die* (once daily)
QOD	*Quaque altera die* (every other day)
Q3 months	*Quaque* (once every 3 months)
Q2W or Q3W	*Quaque* (once every 2 weeks) (once every 3 weeks)
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
RR	Response rate
SAE	Serious adverse event
s.c.	subcutaneous
SD	Stable disease
SHP-1 or SHP-2	Src homology region 2 domain-containing phosphatase-1 or -2
SLM	Study laboratory manual
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBNK	T or B-cell natural killer
TCRβ	T cell receptor beta
TNF	Tumor necrosis factor
TNFα	Tumor necrosis factor alpha
TPC	Tunneled pleural catheter
TPF	Tissue Procurement Facility
TVEC	Talimogene laherparepvec
Txt	Treatment
ULN	Upper limit of normal
UNC	University of North Carolina
USP	United States Pharmacopeia
VEGF	Vascular endothelial growth factor
V-type	Variable-type

TABLE OF CONTENTS

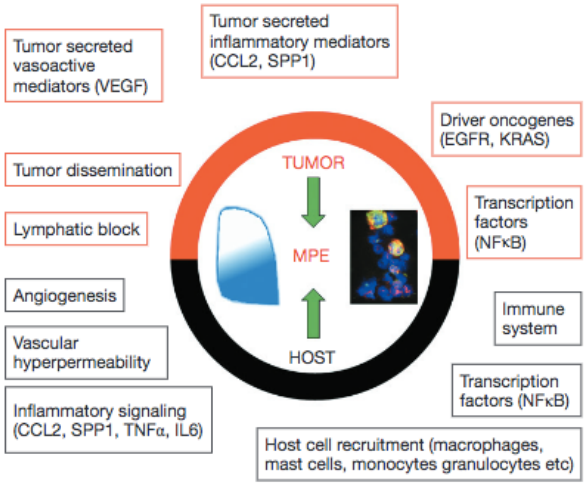
1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

We will conduct a Phase Ib/II trial that includes a safety run-in period using 3 +3 dose escalation rules to evaluate the feasibility of administering talimogene laherparepvec into the intrapleural space of subjects with malignant pleural effusion (MPE) via a pleurX catheter. Initially, 3 patients will be treated with intrapleural talimogene laherparepvec in the first dose cohort. Since this study explores a new route of administration for talimogene lahereparevec, enrollment in the safety run-in cohorts will be staggered requiring each patient to complete the 7-week safety assessment period (i.e., 3 cycles of TVEC including the seroconversion cycle) for evaluation of dose-limiting toxicity (DLT) before the next subject is enrolled. If dose limiting toxicities (DLTs) occur in ≤1 patient treated with talimogene laherparepvec alone, we will treat 3 patients in the second cohort with intrapleural talimogene laherparepvec plus intravenous (IV) nivolumab (240mg). We anticipate reaching the Phase II (combination) dose without significant DLTs or drug toxicities in either cohort, and plan to treat a total of 24 patients with MPE's with intrapleural talimogene laherparepvec and IV nivolumab. The primary endpoint of the study is to determine the rate of resolution of malignant pleural effusion following IV nivolumab combined with intrapleural injection of talimogene laherparepvec. We hypothesize that patients receiving this novel combination will achieve resolution 70% of the time compared to the null hypothesis of 45% with pleur-X catheter alone. In addition, we plan to conduct correlative studies using pleural cytology and blood samples.

1.2 Malignant Pleural Effusions

Pleural fluid normally enters the pleural space through the systemic capillaries of both the parietal and the visceral pleura. It is then removed via lymphatic drainage by osmotic and oncotic gradients through the parietal pleura and by cellular mechanisms [1, 2]. For many years, the major mechanism in the pathogenesis of malignant pleural effusion (MPE) was thought to be associated with tumor blockade of local lymphatic outflow due to tumor dissemination in parietal pleura and mediastinal lymph nodes, which as a result impairs pleural fluid absorption [3, 4]. However, the theory that all MPE form as a result of lymphatic obstruction via tumor blockade has been refuted. Rather, MPE formation constitutes a complex biological process incorporating tumor-host interactions in the vasculature, the immune system and other host cells in the pleural microenvironment, per the figure below (from Spella et al) [1, 5].



Additional mechanisms for MPE formation include increased vascular permeability through excessive plasma leakage [6]. Furthermore, tumor burden in the pleural space leads to hyperpermeable pleural vessels due to increased production of vasoactive mediators such vascular endothelial growth factor (VEGF) and angiopoietins by tumor cells [6]. Host cells have also been shown to contribute to MPE formation via the production of VEGF by transforming growth factor beta in mesothelial cells [7].

A recent interest has been the immune system's role in MPE formation. Proinflammatory mediators like interleukin (IL)-6, tumor necrosis factor (TNF), and chemokine ligand 2 (CCL2) were found to be signaling molecules that triggered MPE formation in mouse models [8-11]. These molecules induce local and regional vascular hyperpermeability, angiogenesis, inflammation and recruit host inflammatory and mesothelial cells to the pleural space, which further secrete proinflammatory molecules leading to MPE development [8, 12]. Finally, tumor signaling attracts host cells, including granulocytes, macrophages, and lymphoids cells, to the pleural space. This tumor-host communication within the pleural space again leads to downstream signaling and the common pathways of inflammation, increased vascular leakage, angiogenesis which mediates MPE formation [13].

Clinically, nearly 50% of patients with metastatic malignancies develop a malignant pleural effusion. More than 80% of these cases are represented by cancers of the lung, breast, gastrointestinal system, ovaries or lymphoma. While malignant mesothelioma is the most common type of primary pleural tumor, lung and breast cancer are the most common malignancies found to be associated with MPE in male and female patients, respectively [1, 14, 15].

The diagnosis of MPE implies advanced disease with median survival of four months, with lung cancer associated with the shortest survival [16]. Currently treatment for MPE centers on palliation of associated symptoms, most commonly

dyspnea and respiratory distress. Palliation of symptomatic malignant pleural effusion consists of serial thoracentesis, chemical pleurodesis and tunneled pleural catheter placement. At this time there are clinical trials aimed at decreasing fluid formation including combination intrapleural bevacizumab (anti-VEGF) and cisplatin therapy for MPE from NSCLC (NCT01661790). These efforts highlight the need for novel approaches to the treatment of MPE.

1.3 PleurX Pleural Catheter System

The PleurX tunneled pleural catheter (TPC) consists of a distally fenestrated silicone catheter with a proximal valve mechanism and a polyester cuff. The valve prevents passage of fluid or air in either direction until it is accessed. The TPC is currently indicated for intermittent, long-term drainage of symptomatic, recurrent pleural effusions including malignant pleural effusions and other pleural effusions refractory to medical management as a result of the underlying disease; in addition to this the TPC has recently been approved for instillation of chemical pleurodesis agents (Talc and Bleomycin)[17]],[18]. A primary goal of our proposed trial is to investigate the novel approach of administering intrapleural talimogene laherparepvec via pleurX catheter in patients with known malignant pleural effusion. A second goal is to demonstrate the potential additive or synergistic effects of local oncolytic viral therapy with systemic immunotherapy. To our knowledge, this is the first study to evaluate local tumor immune microenvironment of malignant pleural effusions.

The PleurX Pleural Catheter is a treatment option for the management of patients with symptomatic recurrent malignant and nonmalignant pleural effusions that do not respond to medical management. Using the PleurX pleural catheter system, patients can manage fluid accumulation through intermittent drainages at home with minimal physician intervention. The PleurX devices are indicated for 1) the palliation of dyspnea due to pleural effusion and 2) providing pleurodesis (resolution of the pleural effusion).

The fenestrated portion of the catheter is inserted into the pleural space utilizing a guidewire needle, guidewire and peel-away introducer (Seldinger technique). The portion of the catheter containing the cuff is tunneled subcutaneously, and the remaining portion is left external to the body. The cuff promotes tissue ingrowth which mitigates the risk of dislodgement and catheter related infection. See **Figure 1** for an illustration of an implanted catheter.

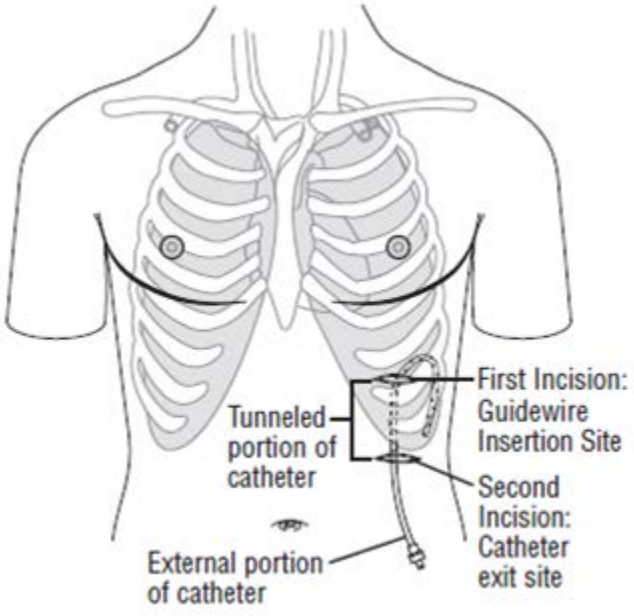


Figure 1 Implanted PleurX Catheter

The catheters are typically placed on an outpatient basis in a hospital or clinic. After implantation, the initial drainage is performed by a clinician utilizing the specially designed drainage line using either wall-suction or vacuum bottles.

Before being discharged, the patient and caregiver are educated by a clinician on how to drain accumulated fluid and take care of the catheter exit site. The drainage kits contain detailed instructions for use written specifically for home care and the necessary items to perform the drainage procedure at home. The patient or caregiver will periodically drain the effusion using the PleurX vacuum bottles in the home setting. Drainage regimens are prescribed by physicians and may include draining daily, bi-weekly, or only as needed.

1.4 Nivolumab (BMS-936558)

Nivolumab is a potent and fully humanized mAb of the immunoglobulin IgG4 that directly blocks the interaction between PD-1 and its ligands, PD-L1 and PDL-2. This blockade enhances functional activity of the target lymphocytes to facilitate an antitumor immune response, leading to tumor regression and immune rejection of the tumor [19, 20]. Opdivo™ (Nivolumab) has been approved in the United States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor. It has also received approval for patients with metastatic non-small cell lung cancer (NSCLC). Current dosing for melanoma therapy and NSCLC is fixed dose of 240mg every 2 weeks. Approval has been granted for patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy (dose is 240mg

every 2 weeks). Nivolumab is under investigation for first line treatment of NSCLC and HNSCC in addition to a variety of other cancer states [21].

1.4.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [22]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [23-27]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene PDCD1) is an immunoglobulin (Ig) superfamily member related to CD28 and CTLA-4 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [28, 29]. The structure of murine PD-1 has been resolved [9]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM).

Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70, all of which are involved in the CD3 T-cell signaling cascade [28, 30-32]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [13; 14]. PD-1 is expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells [33, 34]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [35].

The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [35-38]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory

environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [39]. Although healthy organs express little (if any) PD-L1, a variety of cancers are known to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL) [40]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

1.4.2 Pre-clinical Findings

PD-1 inhibitors like Nivolumab strongly enhance T-lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. In T-cell activation assays using human donor blood cells, the EC50 (concentration where 50% of the maximum effect is achieved) has been reported to be ~0.1 to 0.3 nM. Levels of interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), and other cytokines were modulated by MK-3475. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T-cells [21].

Using an anti-murine PD-1 analog antibody, PD-1 blockade has been shown to significantly inhibit tumor growth in a variety of syngeneic murine tumor models. In these experiments in mice, anti-PD-1 therapy is synergistic with chemotherapeutic agents such as gemcitabine and 5-fluorouracil (5-FU) and combination therapy results in increased complete tumor regression rates in vivo [21].

Since the anti-tumor effect of nivolumab is driven through reactivation of adaptive immune response by blocking PD-1 expressed on T cells, but not direct binding to cancer cells, once the PD-1 on T cells are fully saturated by nivolumab, the shape of the exposure-response relationship among indications is expected to be similar. This is supported by exposure-response analysis in multiple indications. A flat exposure-response relationship was demonstrated between nivolumab exposure (or dose) and efficacy or safety within the dose range 3mg/kg and 240 mg. The similarity in efficacy between the tested dose regimens is further supported by comparisons of overall response rate (ORR)/survival outcomes for the tested dose regimens in the melanoma an HNSCC indications. Available pharmacokinetic results in subjects with various indications (melanoma, NSCLC, HNSCC and MSI-H) support a lack of meaningful difference in PK among tumor types [21].

1.5 Clinical Efficacy of Nivolumab in Humans

Nivolumab is active against human NSCLC and has FDA approval for the treatment of several cancers [41]. In NSCLC, nivolumab as monotherapy led to durable antitumor activity and improved survival in Phase I studies. In a large Phase III study of NSCLC patients who progressed on platinum therapy, nivolumab had longer overall survival compared to docetaxel (12.2 vs. 9.4 months) and

decreased grade 3 and 4 treatment-related adverse events [42]. Most recently, Nivolumab gained approval in HNSCC on 11/10/2016. In 361 patients with recurrent or metastatic HNSCC following platinum based therapy, Nivolumab showed a statistically significant increase in overall survival compared to single agent standard chemotherapy (7.5 vs. 5.1 months) [43].

1.6 Talimogene Laherparepvec

Talimogene laherparepvec is an oncolytic immunotherapy based on a modified clinical strain of HSV-1 that has been designed to selectively replicate in cancer cells. Two HSV-1 genes are deleted, ICP47 and ICP34.5. Deletion of ICP47 allows for the presentation of tumor antigens following oncolytic viral replication and enhances anti-tumor immune responses. Deletion of ICP34.5 leads to functional limitations in non-dividing cells and renders the virus non-pathogenic. The human GM-CSF coding sequence is the inserted and replaces the gene encoding ICP34.5. This prevents recombination between talimogene laherparepvec and wild-type virus. Additionally, expression of GM-CSF results in local GM-CSF production to recruit and activate antigen-presenting cells [44-46]. Talimogene laherparepvec has gained FDA approval for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery [47].

1.6.1 Pharmaceutical and Therapeutic Background

Nonclinical pharmacology studies, including in vitro studies of cytopathic effects and in vivo studies of efficacy in numerous tumor types, have been conducted with talimogene laherparpevec and its murine analog, OncoVEXmouse GM-CSF. Talimogene laherparepvec lyses a variety of in vitro human tumor cell lines in culture including colorectal cancer (HT29), breast cancer (MDA-MB-231), glioblastoma astrocytoma (U-87 MG), prostate adenocarcinoma (LNCaP), and malignant melanoma (SK-MEL-28) tested at a multiplicity of infection between 0.1 and 5; essentially all tumor cells were killed less than 48 hours following infection in vitro [48]. Talimogene laherparepvec affects not only the tumors into which it is injected, but also distant non-injected tumors, demonstrating a systemic beneficial effect from local administration. Talimogene laherparepvec suppresses tumor recurrence upon re-challenge with the same tumor type, and remains effective when animals have undergone previous exposure to wild-type HSV or are immunosuppressed with cyclosporin. Talimogene laherparepvec has been tested to evaluate the combined effects of either radiation or chemotherapy in preclinical studies. Both combinations were tolerated and could support potential clinical studies with these other agents for the treatment of cancer [47].

1.6.2 Pre-clinical Findings

Talimogene laherparepvec has been tested for efficacy both *in vitro* and *in vivo* murine tumor models. It has been shown to eradicate or substantially inhibit tumor growth at doses comparable to those used in clinical studies. Nonclinical evaluation

has also confirmed that GM-CSF enhances the immune response generated, enhancing both injected and uninjected tumor responses.

In a B16 melanoma model, irradiated tumor cells alone did not stimulate significant anti-tumor immunity. However, irradiated tumor cells expressing murine granulocyte-macrophage colony-stimulating factor (GM-CSF) stimulated potent, specific, and durable anti-tumor immunity, requiring both CD4+ and CD8+ cells [49]. In murine models with subcutaneous melanoma, intratumoral G-CSF inoculation with inactivated HSV vectors resulted in greater, dose-dependent tumor inhibition and improved mouse survival compared with HSV alone [50].

A number of pre-clinical studies evaluating the safety of talimogene laherparepvec have been completed. Subcutaneous (SC) in mice mouse, single intra-arterial dose in rat, single intraprostatic dose in dogs, and repeated intravenous (IV) dosing in an embryo-fetal developmental in the BALB/c mouse all demonstrated administration safety and tolerable toxicity profiles. The safety of a surrogate HSV-1 construct expressing murine GM-GSF (OncoVEXmGM-CSF) administered as a repeated SC injection was evaluated in BALB/c mice. High and multiple doses of talimogene laherparepvec were well tolerated in immune competent mice following SC, IV, or intralesional injection. A dose margin based on body weight of 60-fold for general safety is estimated using the no adverse effect level. Similarly, a dose margin of 60-fold (based on body weight) for embryo-fetal development is estimated using the NOAEL (also the highest dose tested in Study 117250) following repeated SC injection in mice compared with the maximum dose to be administered to patients [47].

Key findings following repeated SC administration of talimogene laherparepvec included increased white blood cells, lymphocytes, and neutrophils. There was evidence of transient immune activation (enlargement and increased germinal centers in the spleen, lymphoid hyperplasia in spleen and bone marrow). These effects are consistent with the normal response of animals to administration of a virus, and development of normal anti-viral immunity. As a general rule, mice treated with talimogene laherparepvec tended to seroconvert and develop anti-HSV-1 antibodies. No evidence of overt toxicity to any cell type or organ, and no evidence of virally-associated neuropathology/neurovirulence were observed in talimogene laherparepvec-treated animals.

There is no evidence of virally associated neuropathology/neurovirulence associated with talimogene laherparepvec in any animal treated. Two studies found 10,000-fold less neurovirulence at the median lethal dose (LD50) following intracerebral injection of talimogene laherparepvec with deletion of ICP34.5 as compared to wild-type HSV [51, 52]. Additionally, no mortality was seen in mice treated with intranasal talimogene laherparepvec despite use of doses 100-fold greater than those doses associated with the LD50 for wild-type HSV-1 [53].

1.7 Rationale for Combination of PD-1 Inhibitors with Talimogene Laherparepvec for MPE

Given talimogene laherparepvec's efficacy and favorable toxicity profile as monotherapy, pre-clinical studies have evaluated combining talimogene laherparepvec with other immune-activating agents [54]. In pre-clinical studies in a melanoma mouse model, an oncolytic virus induced both local and distant tumor infiltration with CD4+ and CD8+ T cells. The addition of CTLA-4 blockade induced significant anti-tumor responses and protection from tumor re-challenge [55]. In a phase Ib study, the efficacy of talimogene laherparepvec plus ipilimumab was assessed in advanced melanoma. In 19 patients evaluated, there were no dose limiting toxicities. Objective response rate was 50% with 44% of patients achieving durable response lasting more than 6 months. Additionally, 18 month PFS and OS were 50% and 67%, respectively [56].

Currently, combination therapy with talimogene laherparepvec and pembrolizumab is being investigated in two human populations: unresected melanoma and recurrent metastatic HNSCC. A two-part phase 1b/3 studying is being conducted in patients with unresectable stage IIIB-IV melanoma to evaluate the safety of talimogene laherparepvec in combination with pembrolizumab versus pembrolizumab alone. The phase 1b portion of the study was single armed evaluating safety of talimogene laherparepvec and pembrolizumab combination. Twenty-one patients received intralesional injections of talimogene laherparepvec on a dose-escalation basis up to ≤4 mL at 10^8 PFU/mL dose every 2 weeks. Pembrolizumab 240mg IV every 2 weeks was initiated at 5 weeks after the initial talimogene laherparepvec dose. Treatment was continued until disease progression per immune-related response criteria (irRC), no injectable lesions, study treatment intolerance, or 2 years of treatment. No DLTs were reported and seven patients reported treatment-related Grade 3 adverse events. Of the 21 patients in the phase 1b study, results yielded confirmed ORR (57.1%), CR rate by irRC (23.8%), and disease control rate (71.4%). The phase 3 study investigating the safety and efficacy of talimogene laherparepvec in combination with pembrolizumab versus pembrolizumab alone is currently underway [47, 57]. Additionally an NCI-led Phase II trial has been proposed for combination talimogene laherparepvec and nivolumab in refractory T-cell lymphoma and advanced non-melanoma skin cancers.

Based on these observations, we propose to conduct a Phase II trial that includes a safety run-in cohort to investigate the novel approach of administering intrapleural talimogene laherparepvec via a pleurX catheter in patients with known MPE. After establishing the safety of this approach, we plan to treat a total of 24 patients with MPE's with intrapleural talimogene laherparepvec and IV nivolumab. We hypothesize that patients receiving this novel combination will achieve resolution 70% of the time compared to the null hypothesis of 45% with pleur-x catheter alone. In addition, we plan to conduct correlative studies using pleural cytology and blood samples as outlined below.

In clinical practice, chemotherapy (bleomycin) and irritant agents (such as talc) have been administered to the pleural space. Out of an abundance of caution, we conduct a phase I study as described to ensure safety while infusing talimogene laherparepvec. However, we note that knowledge of the mechanism of action and previous safety data with subcutaneous injection suggest low risk of novel adverse events from this mechanism of injection. Further, phase I data of the combination of subcutaneous talimogene laherparepvec further support the safety of this combination [58].

1.8 Correlative Studies

We hope to define changes in the tumor immune microenvironment elicited by combination of intrapleural talimogene laherparepvec and IV Nivolumab therapy in patients with maligant pleural effusions. The tumor immune microenvironment is a complex mixture of competing cellular phenotypes. Thus an optimal predictor of response to immunomodulatory therapy will likely include features that describe tumor genetics, tumor-related immunosuppression, and any existent but insufficient anti-tumor immune response. Correlative studies will be run in both pleural fluid and blood samples.

We hypothesize that (1) patients treated with nivolumab + talimogene laherparepvec will show increased effector lymphocytic infiltrates, decreased regulatory cell populations, and increased clonal expansion of tumor-infiltrating T cells; moreover, (2) a robust integrated model that predicts response vs. resistance can be made from a set of key clinical, tumor, and immune features.

1.8.1 Aim 1

Pleural fluid and blood samples will be analyzed by flow cytometry at three time points: pre-treatment, 3 weeks post initial therapy, and 9 weeks post initial therapy. Pleural fluid derived single-cell suspensions will be stained with fluorescently-labeled antibodies to quantify cytotoxic T cells , effector helper T cells , and regulatory T cells. Regulatory T cells will also be sub-fractionated into naïve, effector, effector memory , and central memory . T cells will also be analyzed for the expression of regulatory proteins PD1 and CTLA4. B cells will be quantified as naïve vs. activated.We will also quantify myeloid-derived suppressor cells and tumor-associated macrophages . Non-naïve T cells and B cells will be sorted and TCRβ/IgH repertoires will be amplified and sequenced. Lymphocyte subset frequencies and TCRβ/IgH repertoires from peripheral blood will be evaluated for similarity with tumor and controls using the Morisita-Horn index and Kruskal-Wallis significance testing.

1.8.2 Aim 2

We will perform RNA sequencing and whole exome sequencing (WES) to analyze the tumor and local pleural immune microenvironment by gene expression profiling on pre-treatment samples. RNA and DNA will be extracted from pleural fluid samples. mRNA-Seq libraries will made and sequence data will be processed,

filtered, and aligned and transcript abundance quantitated. DNA libraries will be made to perform whole exome sequencing. Determination of molecular subtypes and relative expression of gene signatures associated with immune cellular and functional phenotypes along with inference of T cell and B cell receptor repertoire characteristics from mRNA-seq data will be performed. We will consider the following features as potential determinants of response: age, performance status, smoking status, tumor type and histology, total dose of nivolumab and talimogene laherparepvec received, molecular subtype, expression of PD-1 ligands, expression of immune phenotypic gene signatures, and TCRβ/IgH repertoire characteristics.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

2.1.1 Phase I: Characterize the safety and tolerability of intrapleural injection of talimogene laherparepvec alone and in combination with IV nivolumab

2.1.2 Phase II: Resolution (≤50cc drainage over three consecutive every other day drainages) of pleural fluid accumulation accompanied by patient-defined improvement in symptoms (dyspnea, cough and/or chest pain)..

2.2 Secondary Objectives

2.2.1 Estimate progression free survival (PFS) following nivolumab and talimogene laherparepvec per irRECIST.

2.2.2 Estimate overall survival (OS).

2.2.3 Estimate rates of response (RR) via irRECIST.

2.2.4 Further characterize the toxicity profile of intrapleural talimogene laherparepvec administered alone and in combination with IV nivolumab (Phase II).

2.2.5 Describe modified Borg Scale of Perceived Dyspnea over the course of therapy (Provided in 11.6 **Appendix F: Borg Scale**).

2.3 Exploratory Objectives

Via multi-parametric flow cytometry and mRNA-sequencing methods:

2.3.1 Explore tumor molecular subtype and immune gene expression signatures

2.3.2 Explore comprehensive T-cell quantification and phenotyping, including the change in effector lymphocytic infiltrates, regulatory T cell populations, and clonal expansion of tumor-infiltrating T cells

2.3.3 Explore if it is possible to predict signature response vs. resistance expression from key clinical, tumor, and immune features.

2.3.4 Measure expression of PD-1, PD-L1, PD-L2, and other immune check point molecules

2.4 Study Endpoints

2.4.1 Primary Endpoint

2.4.1.1 Phase I**:** Clinician assessed toxicity will be classified and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 5.0).

2.4.1.2 Phase II: **Resolution (≤50cc drainage over three consecutive every other day drainages) of pleural fluid accumulation accompanied by patient-defined improvement in symptoms (dyspnea, cough and/or chest pain).**

2.4.2 Secondary Endpoints

2.4.2.1 Median PFS. PFS will be defined as the time from D1 of treatment until death or progression.

2.4.2.2 Median OS. OS is defined as the time from D1 of treatment to death from any cause.

2.4.2.3 Tumor response will be defined as the proportion of patients with reduction in tumor (irCR+irPR) per irRECIST criteria outlined in section 6.8.

2.4.2.4 Clinician assessed toxicity will be classified and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 5.0).

2.4.2.5 Use of modified Borg rating scale for perceived dyspnea (10 point scale from 1 to 10 which measures perception of dyspnea) [59, 60] (Provided in 11.6 **Appendix F: Borg Scale**).

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria to participate in this study:

3.1.1 Signed a written IRB-approved informed consent and HIPAA authorization for the trial.

3.1.2 Be ≥ 18 years of age on day of signing informed consent.

3.1.3 ECOG Performance Status ≤ 2. (See Appendix A: ECOG Performance Status).

3.1.4 Histologically or cytologically confirmed stage IV metastatic cancer.

3.1.5 Confirmation of malignant pleural effusion via imaging (CXR, CT scan, ultrasound, MRI, or PET/CT) and cytology for which pleurX catheter placement is standard of care.

- Dose Level 1: Either no systemic therapy available per standard of care, or delay in administration of systemic therapy considered clinically acceptable.

- Dose Level 2/Phase II: Nivolumab alone would be an acceptable standard treatment OR have a tumor type with prior data for PD1 efficacy OR non-pleural disease is not considered a significant risk to the patient OR refractory to standard therapies.

3.1.6 Demonstrate adequate organ function as defined in the table below. All screening labs should be performed within 14 days of treatment initiation.

System	Laboratory Value[2]
Hematological	
Absolute neutrophil count (ANC)	≥1000 /μL
Platelets	≥50,000 / μL
Hemoglobin	≥10 g/dL (acceptable to reach this through transfusion)
Renal	
Calculated creatinine clearance (Cockcroft-Gault)[1]	≥45 mL/min
Coagulation	
INR or PT	≤ 1.5 x ULN unless the subject is receiving anticoagulant therapy, in which case PT and PTT/aPTT must be within therapeutic range of intended use of anticoagulants
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	>2.5 mg/dL
Pulmonary	
Pulse Oximetry	At least 90% on room air (**OR** 95% on oxygen)
Cardiac	
EKG	No clinically relevant cardiac dysfunction
Troponin	< 0.3

System	Laboratory Value[2]

1. **See Appendix B (Section 11.2) for Cockcroft-Gault formula.**
2. Hematology and other lab parameters that are ≤ grade 2 BUT still meet criteria for study entry are allowed. Furthermore, changes in laboratory parameters during the study should not be considered adverse events unless they meet criteria for dose modification(s) of study medication outlined by the protocol and/or worsen from baseline during therapy.

3.1.7 Recovered from all reversible toxicities related to their previous treatment (other than alopecia) to ≤grade 1 or baseline; exceptions to this criterion may be allowed following review by the principal investigator for toxicities that are not expected to be exacerbated by nivolumab or talimogene laherparepvec. Grade 2 peripheral neuropathy will not result in exclusion as neither study agent would be expected to exacerbate it.

3.1.8 No history of untreated brain metastasis. Treated brain metastases must not be known to be progressive, symptomatic, or currently requiring > 10 mg of prednisone or prednisone equivalents within two weeks prior to study drug administration.

3.1.9 Females of childbearing potential must have a negative serum pregnancy test within 72 hours prior to receiving the first dose of study medication. Females of childbearing potential must agree to use 2 methods of effective contraception or abstain from heterosexual sex throughout the treatment period and for 5 months after the last dose of study treatment. Females of childbearing potential are women who have not been surgically sterilized (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or have not been free of menses for >1 year.

3.1.10 Male patients with female partners must have had a prior vasectomy or agree to use an adequate method of contraception (i.e. double barrier method: condom plus spermicidal agent) starting with the first dose of study therapy through 7 months after the last dose of study treatment.

3.1.11 As determined by the enrolling physician or protocol designee, ability or willingness of the patient to understand and comply with study procedures.

3.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria will not be able to participate in this study:

3.2.1 Receiving any investigational agent, or using an investigational device, currently or within 28 days or 5 half-lives of Day 1 of treatment on this study, whichever is longer.

3.2.2 Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1.

3.2.3 Has had a prior monoclonal antibody within 4 weeks prior to study Day 1, or who has not recovered to, ≤ Grade 1 toxicity at baselines from adverse events due to agents administered more than 4 weeks earlier. Exceptions to these criteria may be allowed at the discretion of the investigator for toxicities that are not expected to be exacerbated by nivolumab or talimogene laherparepvec (e.g., alopecia, peripheral neuropathy, etc).

3.2.4 Any concurrent chemotherapy, IP, biologic or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.

3.2.5 Major surgery within 28 days prior to day 1 of study treatment from which the patient has not completely recovered.

3.2.6 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.

3.2.7 Has a known secondary malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.

3.2.8 Has an active automimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents; subjects with resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study. 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. Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.

3.2.9 Has a history of non-infectious pneumonitis that required steroids; currently active non-infectious pneumonitis; or evidence of interstitial lung disease.

3.2.10 Has an active infection requiring systemic therapy or history of uncontrolled infection.

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

known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. This also includes unstable angina, serious uncontrolled cardiac arrhythmia, uncontrolled infection, or myocardial infarction ≤ 6 months prior to study entry.

3.2.12 Has inadequate home environment or social support to safely complete the trial procedures.

3.2.13 Is pregnant or breastfeeding.

3.2.14 Known human immunodeficiency virus (HIV), hepatitis C virus (HCV) or evidence of active hepatitis B virus (HBV).

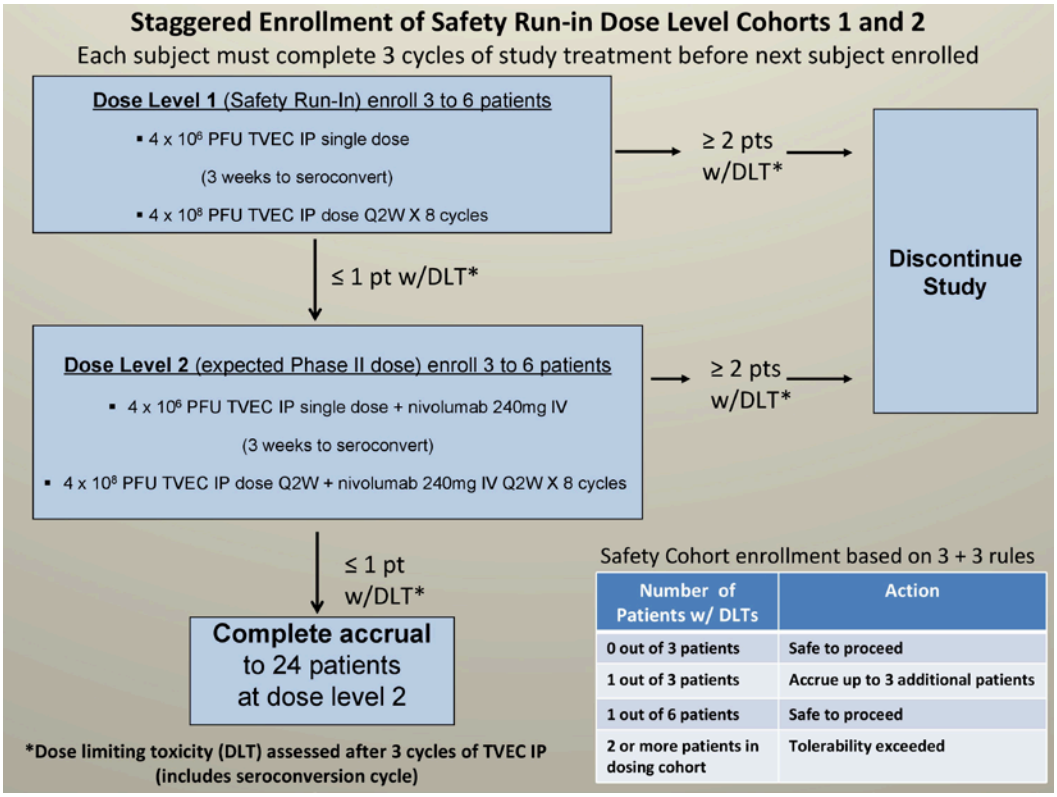
3.2.15 Has a multi-loculated pleural effusion that would not lead to relief of dyspnea from drainage of a single loculation.

3.2.16 Current active hepatic or biliary disease (with exception of patients with Gilbert's syndrome, asymptomatic gallstones, or stable chronic liver disease per investigator assessment).

3.2.17 Active herpetic skin lesions or prior complications of herpetic infection or requires intermittent or chronic systemic (intravenous or oral) treatment with an antiherpetic drug (e.g., acyclovir), other than intermittent topical use.

4.0 TREATMENT PLAN

4.1 Schema for LCCC 1626



Talimogene laherparepvec (TVEC) will be given intrapleural (IP) instillation for up to 9 cycles (includes seroconversion dose 4ml of10^6 pfu/mL) in Dose Level cohorts 1 and 2. Nivolumab (240 mg IV) will be co-administered with talimogene laherparepvec (4ml of 10^8 pfu/mL) for up to 9 cycles in the Dose Level 2 cohort, with 3 week interval between cycle 1 and cycle 2 to allow for seroconversion. Patients will be allowed to continue nivolumab monotherapy per standard of care (240 mg IV Q2W) as long as they are responding to therapy (i.e., until disease progression, untoward toxicity, or withdrawal for other reasons).

This Phase Ib/II trial includes a safety run-in period using 3 + 3 dose escalation rules to evaluate the feasibility of administering talimogene laherparepvec into the intrapleural space of patients with MPE via a pleurX catheter. All infusions of talimogene laherparepvec will occur in 200cc normal saline (NS) followed by 20cc of sterile saline to clear the catheter, regardless of dose. Subjects will be instructed to avoid drainage for at least 24 hours, then to drain the catheter (and flush with 20 cc of sterile saline) when next needed to palliate shortness of breath, consistent with standard of care use of the pleurX catheter. If a patient becomes dyspneic <24 hours after talimogene laherparepvec administration, they should consult the interventional pulmonology team at UNC to determine if catheter drainage is necessary. Patients who experience severe shortness of breath <24 hours after

intrapleural talimogene laherparepvec will be allowed to have their catheter drained.

4.1.1 Cohort Enrollment – Safety Run-in

Since this is the first time talimogene lahereparevec is being given in the intrapleural space (i.e. new route of administration), enrollment in safety run-in cohorts 1 and 2 will be staggered. Each subject will be required to complete the 7-week safety assessment period (i.e. 3 cycles of TVEC including the seroconversion cycle) of dose-limiting toxicity (DLT) before the next subject is enrolled. During the safety run-in period starting in Dose Level 1, patients will only receive intrapleural talimogene laherparepvec . The first dose of talimogene laherparepvec will be administered on Cycle 1, Day 1 at 4ml of 10^6 pfu/mL in 200 cc normal saline (intrapleurally) to seroconvert HSV-seronegative patients. Three weeks will be given for seroconversion. Subsequent doses of talimogene laherparepvec at 4ml of 10^8 pfu/mL will then be administered IP every two weeks (Q2W) starting on Cycle 2, Day 1 for up to 8 cycles. Patients will be assessed for dose limiting toxicity (DLT) related to IP administration of talimogene lahareparepvec after they have completed at least 3 cycles (i.e. 7 weeks) of monotherapy. If ≥2 patients experience DLT, the study will be discontinued. If 1 patient out of 3 has DLT, 3 additional patients will be recruited and treated at the same dose level. If 0 out of 3 patients or ≤ 1 patient out of 6 has a DLT, the study will proceed to Dose Level 2. One week following completion of study therapy, subjects may proceed to systemic therapy per their decision with their physician.

In Dose Level 2 (expected Phase II dose), the first 3 patients will receive both IP talimogene laherparepvec and IV nivolumab. The first dose of talimogene laherparepvec will be administered on Cycle 1, Day 1 at 4mL of 10^6 pfu/mL in 200 cc normal saline (IP) to seroconvert HSV-seronegative patients. Three weeks will be given for seroconversion. Subsequent doses of talimogene laherparepvec at 4ml of 10^8 pfu/mL + Nivolumab 240 mg IV will be administered every two weeks starting on Cycle 2, Day 1 for up to 8 cycles of therapy. Patients will be assessed for DLTs related to IP administration of talimogene lahareparepvec after seroconversion and 2 cycles of combination therapy (i.e.,7 weeks of study treatment). If ≥2 patients experience DLT, the study will be discontinued. If 1 patient out of 3 has DLT, 3 additional patients will be recruited and treated at the same dose level. If 0 out of 3 or ≤ 1 patient out of 6 has a DLT in the dose level 2 cohort, the study will recruit additional patients in Phase II at this dose level and accrue a total of 24 patients as per study goal. All patients treated at dose level 2 in Phase I or Phase II, will be included in analyses of safety and efficacy. Safety stopping rules will ensure the safety of subjects receiving combination treatment in Phase II (see Statistical Considerations in section 9.0.)

Subjects may continue talimogene laherparepvec for up to 9 cycles (i.e. alone or with nivolumab) until resolution of pleural effusion or they experience systemic disease progression. Subjects who have resolution of pleural effusion as defined by

the primary endpoints may continue nivolumab monotherapy per standard of care until disease progression (see section 4.2 for details on treatment and section 6.5.2).

4.1.2 TPC drainage

Tunneled pleural catheter drainage during both Phase Ib/II will occur as follows:

Standard Drainage -
Drainage will take place either in the subject's home or in a suitable clinical area. All drainages after placement should be performed using standard aseptic technique and, unless connected to an inpatient drainage device, should be performed using PleuX vacuum drainage bottles. All drainage volumes should be recorded in the subject's diary. The subject must contact the clinical site once he/she has drained <50mL on 3 consecutive drainages performed every other day.

Study Drug Drainage -
Following IP infusion of TVEC via the TPC, patients will allow the product to dwell for 24 hours. After 24 hours the patients will drain their TPC either fully or up to the point of symptom development (chest pain/pressure, progressive dyspnea, intractable coughing). Following drainage of the dwelled product, the patients will follow an every other day (QOD) drainage schedule. Patients will drain as fully as possible, stopping at the point of symptom development.

In the event patients develop dyspnea after IP infusion of TVEC they will be allowed to drain their TPC earlier than 24 hours.

4.1.3 Definitions of Dose Limiting Toxicities (DLT) – Safety Run-in

A DLT is defined as the development of any new non-hematologic treatment-related grade 3-5 adverse event during or up to 14 days following the third IP dose of talimogene laherparepvec. This results in a 7 week DLT period.

- All subjects with grade 4 DLT events will be permanently discontinued from the study
- All subjects with ≥ grade 3 DLTs of myocarditis or pneumonitis will be permanently discontinued from the study
- I.e., if > 1 scheduled dose of talimogene laherparepvec is missed due to study treatment-related toxicity, talimogene laherparepvec will be permanently discontinued and this event will be considered a DLT

The following adverse events are considered exceptions:

- Grade 3 laboratory-defined events that are asymptomatic and resolve without permanent sequelae to grade 0-1 within a week (ex. a grade 3 LFT

elevation that occurs in the absence of symptoms, resolves to G1 within a week and does not result in any change in liver function).

- Alkaline-phosphatase elevation in patients with known bone metastases
- Pneumothorax, catheter-related complications or other intrapleural effects that are attributed to the standard of care catheter, disease state, or pre-existing medical problems that are not unexpected.
- G3 diarrhea or nausea that resolve to G1 or lower within 48 hours
- Any grade 3-infusion/hypersensitivity reaction symptoms that resolve to grade 0-1 with dose interruption, infusion rate reduction, or supportive care.
- Reactions attributed to nivolumab alone that would be expected in standard of care use may result in permanent cessation of treatment for an individual patient, but will not result in a DLT. Such a patient will be replaced. (Example: an infusion reaction of grade 3 to nivolumab consistent with that occasionally seen in standard of care use).
- Tumor lysis syndrome
- Any AE determined to be unrelated to study treatment
- Events related to disease progression/relapse

In addition, the following will be considered DLTs when treatment-related:

- Pleuritic pain refractory to opioid therapy
- Acute respiratory distress syndrome

4.1.4 Safety Assessment Period - Safety run-in:

The safety assessment period for DLT assessment encompasses 3 cycles of study treatment (i.e. 7 weeks total). Three weeks will be given for seroconversion following the first dose of talimogene laherparevec (4 x 10^6 pfu). Subsequent doses of talimogene laherparepvec (4 x 10^8 pfu) will be given alone or with nivolumab (240 mg IV) every two weeks starting on Cycle 2, Day 1 for up to 8 cycles of therapy. Patients will be assessed for DLTs after seroconversion and 2 cycles of talimogene lahareparepvec given alone or with nivolumab every 2 weeks. Cohorts will be enrolled according to 3+3 rules and each subject must complete the safety assessment period before the next patient is treated (see above study schema). If ≥2 patients experience DLT in a dose cohort, the study will be discontinued.

4.2 Study Treatments

Agent	Pre-medications	Dose/Frequency	Route	Schedule
talimogene laherparepvec (1st dose only)[1]	30 min prior to IP talimogene laherparepvec give anti-pyretic & anti-nausea meds (e.g., 500 mg acetaminophen & 10 mg prochlorperazine)	4x10^6 pfu; next dose of talimogene laherparepvec given 3 weeks later	via pleurX catheter and allow product to dwell for at least 24 hours	D1 cycle 1 only; subsequent dose given three weeks later
talimogene laherparepvec (Subsequent doses)[1]		4x10^8 pfu every 2 weeks X 8 doses	via pleurX catheter and allow product to dwell for at	D1 cycle 2 of study for up to 8 cycles given every 2 weeks (14 days)

			least 24 hours	until fluid stops re-accumulating (i.e., resolution of pleural effusion) or until systemic disease progression
Nivolumab	See section 4.3.3 for management of infusion-related reactions associated with nivolumab	240 mg every 2 weeks	IV over 30 minutes	Starting on D1 of Cohort 2 Dose Level 2 and beyond; Every 2 weeks (14 days) until disease progression (per RECIST or irRC) or withdrawal for other reasons

1. See Appendix D -Information Sheet for Caregivers, Family Members or other Close Contacts to Clinical Trial Participants being given Talimogene Laherparepvec).

Talimogene laherparepvec (4 mL) at a concentration of 10^6 (1 million) plaque-forming units (pfu)/mL will be administered into the pleurX catheter for a total dose of 4 X10^6 pfu for the first dose. Subsequently, talimogene laherparepvec (4 mL) at a concentration of 10^8 (100 million) pfu/mL will be administered every two weeks into the pleurX catheter. Dosing with talimogene laherparepvec will be continued until pleural fluid stops re-accumulating or until systemic disease progression. Subjects who have resolution of pleural effusion as defined by the primary endpoints may continue nivolumab monotherapy per standard of care until disease progression. The dose rationale for talimogene laherparepvec therapy is based on the OPTiM trial in melanoma and subsequent analysis [44, 61].

All IP infusions of talimogene laherparepvec will be in 200cc NS followed by 20cc of sterile saline to flush the catheter. Subjects will be instructed to allow the product to dwell for at least 24 hours after which they should next drain the catheter when next needed to palliate shortness of breath, consistent with standard of care use of the catheter. Subjects or their caregivers will be instructed to use medical gloves when draining the catheter and to avoid physical contact with fluid drained from the catheter. Standard drainage bottles will be used. Subjects will be allowed to either add bleach to the bottle then dispose per standard procedures or return to the investigators for disposal. These precautions will be advised permanently after study initiation (**See Appendix D -Information Sheet for Caregivers, Family Members or other Close Contacts to Clinical Trial Participants being given Talimogene Laherparepvec**).

Nivolumab 240 mg will be administered (per standard of care) as a 30-minute IV infusion on D1 of each cycle every two weeks.

Nivolumab and talimogene laherparepvec may be administered in either order. Administration of the two agents should be within 30 hours of each other.

4.3 Dose Modifications/Delays

4.3.1 Talimogene laherparepvec Dose Modifications/Delays

There will be no dose modifications allowed for talimogene laherparepvec during the study. Talimogene laherparepvec will be administered as described in section 4.2 above. Talimogene laherparepvec administration will either be withheld or permanently discontinued depending on the severity of event related to its administration. If a grade 4 DLT occurs, talimogene laherparepvec will be permanently discontinued. If grade 3 DLTs occur with talimogene laherparepvec administration as described in section 4.1.2 (Definition of DLTs), the next dose of talimogene laherparepvec will be withheld and will not be given until symptoms have resolved to ≤ grade 1. If > 1 scheduled dose of talimogene laherparepvec is missed due to toxicity, talimogene laherparepvec will be permanently discontinued.

Doses up to 4 mL at dose strength of 10^8 pfu/mL every 2 weeks (maximum cumulative dose of 222.5 x 10^8 pfu) have been administered in clinical studies, with no evidence of DLT. The maximum cumulative dose of talimogene laherparepvec planned for this trial is 9 total administrations (including initial seroconversion dose). See section 5.1.6, for warnings and precautions related to talimogene laherparepvec administration. Patients may receive premedication with an anti-pyetic and anti-nausea medication (e.g., acetaminophen 500mg PO and prochloraperizine 10mg PO) prior to every talimogene laherparepvec injection.

4.3.2 Nivolumab Dose Modifications/Delays

Toxicity grades per NCI-CTCAE Criteria v5.0

Adverse Reaction	Severity	Dose Modification
Colitis	Grade 2 diarrhea or colitis	Withhold dose[a]
	Grade 3 diarrhea or colitis	Withhold dose[a] when administered as a single agent
		Permanently discontinue when administered with ipilimumab
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose[a]
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hepatitis/non-HCC[b]	Aspartate aminotransferase (AST)/ or alanine aminotransferase (ALT) more than 3 and up to 5 X the ULN or total bilirubin > 1.5 and up to 3X ULN	Withhold dose[a]
	AST or ALT more than 5X ULN or total bilirubin > 3X ULN	Permanently discontinue
Hepatitis/HCC[b]	If AST/SLT is within normal limits at baseline and increases to more than 3 and up to 5 times the ULN or total bilirubin more than 1.5 and up to 3 times the ULN If AST/ALT is more than 1 and up to 3	Withhold dose[c]

	times ULN at baseline and increases to more than 5 and up to 10 times the ULN If AST/ALT is more than 3 and up to 5 times ULN at baseline and increases to more than 8 and up to 10 times ULN	
	If AST/ALT is more than 3 and up to 5 times ULN at baseline and increases to more than 8 and up to 10 times the ULN	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose[a]
	Grade 4 hypophysitis	Permanently discontinue
Adrenal insufficiency	Grade 2 adrenal insufficiency	Withhold dose[a]
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose[a]
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6X ULN	Withhold dose[a]
	Serum creatinine more than 6X ULN	Permanently discontinue
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose[a]
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose[a]
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction First occurrence Recurrence of same Grade 3 adverse reaction	Withhold dose[a] Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Grade 3 myocarditis	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

a) Resume treatment when adverse reaction returns to Grade 0 or 1.
b) HCC: hepatocellular carcinoma
c) Resume treatment when AST/ALT returns to baseline.

4.3.2.1 Dose Delay Criteria for Nivolumab

Because of the potential for clinically meaningful nivolumab-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected AEs of selected categories [see Appendix C section 11.3].

Dose delay criteria apply for all drug-related AEs. Nivolumab must be delayed until treatment can resume.

Nivolumab administration should be delayed for the following:
Any Grade ≥ 2 non-skin, drug-related AE, with the following exceptions:

- Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related AE

Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, total bilirubin, or asymptomatic amylase or lipase:

- Grade 3 lymphocyte count decreased or white blood cell decreased does not require dose delay.
- If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
- If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
- Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The Investigator should be consulted for such Grade ≥ 3 amylase or lipase abnormalities.

Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, warrants delaying the dose of study medication.

4.3.2.2 Criteria to Resume Nivolumab Treatment

Subjects may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if investigator allows.
- Subjects with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment if the investigator allows it, but this should be documented clearly in the electronic case report form (eCRF).

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol, the next scheduled time point will be delayed until dosing resumes.

If treatment is delayed or interrupted for > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in the discontinuation section.

4.3.2.3 Management Algorithms for Nivolumab

Guidelines for the management of immune-related events can be found in the approved United States Product insert.

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered an I-O agent in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity.

Management algorithms (See Appendix C, section 11.3) have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal,
- Renal,
- Pulmonary,
- Hepatic,
- Endocrinopathies,
- Skin, and
- Neurological.

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an AE, consider recommendations provided in the algorithms. These algorithms are found in the Nivolumab IB and in Appendix C, section 11.3 of this protocol. The guidance provided in these algorithms should not replace the Investigator's medical judgment but should complement it.

4.3.2.4 Discontinuation Criteria for Nivolumab

Treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation

  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except those noted below
- Grade 3 drug-related platelet count decreased > 7 days or associated with bleeding requires discontinuation
- Any drug-related hepatic abnormality that meets the following criteria require discontinuation:
  - AST or ALT > 8 x ULN
  - Total bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 lymphocyte count decreased or white blood cell decreased
  - Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Investigator
- Any dosing interruption lasting > 6 weeks with the following exceptions:
  - Dosing delays or interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted or delayed
  - Dosing interruptions or delays lasting > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted
- Permanently discontinue nivolumab for grade 3 myocarditis

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing

4.3.3 Management of Nivolumab Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms of allergic-like reactions.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAEv5.0 guidelines.

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

For Grade 1 symptoms during nivolumab infusion: (Mild reaction; infusion interruption not indicated; intervention not indicated). Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms during nivolumab infusion: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, non-steroidal anti- inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for 24 hours).

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms during nivolumab infusion: (Severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; pressor or ventilatory support indicated).

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

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

4.4 Concomitant Medications/Treatments

Patients on the trial are allowed to receive all supportive care therapy needed to alleviate symptoms related to their cancer diagnosis or other medical problems at the investigator's discretion. No treatments should be withheld due to a patient's participation in this study. Prophylaxis for infusion-related reactions should be employed per institutional guidelines (also refer to Section 4.3.3).

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 Bristol-Meyers-Squibb (BMS) Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

4.4.1 Special warnings and precautions

- Nivolumab is associated with immune-related AEs. Subjects should be monitored continuously as an AE with nivolumab may occur at any time during or after discontinuation of therapy.

- For suspected immune-related reactions, adequate evaluation should be performed to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab should be withheld and corticosteroids administered. If immunosuppression with corticosteroids is used to treat an AE, a taper of at least 1-month duration should be initiated upon improvement. Rapid tapering may lead to worsening of the AE. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use.

4.5 Duration of Therapy

In the absence of treatment delays due to AEs, treatment may continue until the end of study-defined treatment or until:

- Disease progression (Note: treatment may continue until progression is confirmed by repeat scan approximately 6 weeks later to rule out pseudoprogression based on investigator discretion)
- Inter-current illness that prevents further administration of treatment
- Unacceptable toxicity
- Pregnancy
- Patient decides to withdraw from study treatment, **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.6 Duration of Follow Up

After stopping study therapy, subjects should be followed as described in the time and events table in Section 6.0 and in the follow up section in 6.5. After two years of follow-up as described in the time and events tables, subsequent follow-up will be per standard of care. Subjects can be contacted by phone or followed via medical records every 3 months (+/- 15 days) for follow up information on disease progression and survival until death.

4.7 Removal of Patients from Protocol Therapy

Patients will be removed from protocol therapy and the PI notified when any of the criteria listed in section 4.5 apply. The reason for discontinuation of protocol therapy will be documented on the eCRF.

In case a patient decides to prematurely discontinue protocol therapy ("refuses treatment"), the patient should be asked if she or he may still be contacted for further scheduled study assessments or have relevant information on PFS and OS accessed from their medical record. The outcome of that discussion should be documented in both the medical records and in the eCRF.

Excessive patient withdrawals from protocol therapy or from the study can render the study un-interpretable; therefore, unnecessary withdrawal of patients should be avoided.

4.8 Study Withdrawal

If a patient decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. The investigator should contact the patient or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the study withdrawal. A complete final evaluation at the time of the patient's study withdrawal should be made with an explanation of why the patient is withdrawing from the study. If the reason for removal of a patient from the study is an adverse event, the principal specific event will be recorded on the eCRF.

5.0 DRUG INFORMATION

5.1 Talimogene Laherparepvec (Imlygic™)

Please refer to the Talimogen laherparepvec pharmacy information guide for additional information.

5.1.1 Description

Talimogene laherparepvec is a sterile suspension of live, attenuated herpes-simplex virus -1 (HSV-1) that has been genetically modified to express huGM-CSF. The parental virus for talimogene laherparepvec was a primary isolate, which was subsequently altered using recombinant methods to result in gene deletions and insertions.

5.1.2 Supplier/How Supplied

Talimogene laherparepvec will be presented as a sterile, semi-translucent to opaque solution for injection (opacity is different for each concentration) preservative-free frozen liquid in a single use 2 mL cyclic olefin polymer (COP) plastic resin vial. Each vial will contain talimogene laherparepvec at a nominal concentration of 10^6 PFU/mL or 10^8 PFU/mL in an aqueous sodium phosphate buffer with sodium chloride, sorbitol and myo-inositol added as stabilizers and water for injection (WFI). Vials are appropriately filled to ensure that a sufficient deliverable dose is provided. Each 2 mL vial will contain approximately 1.15 mL of talimogene laherparepvec with a 1.0 mL deliverable volume. Each vial is intended for single use only.

Vials will be sealed with gray rubber stoppers, fluorotec-coated on the product side. The vial caps will be color coded and may be used to help distinguish between the 10^6 PFU/mL and 10^8 PFU/mL vial concentrations. The supply for 10^6 PFU/mL vials will be packaged separately from the supply for the 10^8 PFU/mL vials.

- The 10^6 PFU/mL strength is supplied in a box containing 10 vials.
- The 10^8 PFU/mL strength is supplied in a box containing 20 vials.

For additional information please refer to the talimogene laherparepvec pharmacy information guide.

5.1.3 Storage, Handling and Dispensing

Talimogene laherparepvec must be stored in a non-cycling freezer maintained at a set point of -80°C in a secured location until planned use. Cycling, frost-free, auto defrost freezers must not be used since they cycle to warmer temperatures several times a day. Vials should be kept within the secondary container to protect from light. The table below outlines the storage temperature requirements.

Storage of Talimogene Laherparepvec - Freezer Set Point

Freezer Set Point (°C)	Acceptable Variation	Acceptable Range
-80°C	**± 10°C**	**-90°C to -70°C**

All infusions of talimogene laherparepvec will be in 200cc NS followed by injection of 20cc sterile saline to clear the catheter. Subjects will be instructed to allow the product to dwell for at least 24 hours after which they should next drain the catheter when next needed to palliate shortness of breath, consistent with standard of care use of the catheter. Subjects or their caregivers will be instructed to use medical gloves when draining the catheter and to avoid physical contact with fluid drained from the catheter. Standard drainage bottles will be used. Subjects will be allowed to either add bleach to the 60 cc syringe or bottle and then dispose per standard procedures or return to the investigators for disposal. These precautions will be advised permanently after study initiation (**See Appendix D - Information Sheet for Caregivers, Family Members or other Close Contacts to Clinical Trial Participants being given Talimogene Laherparepvec**).

5.1.4 Preparation

All personnel handling talimogene laherparepvec or material contaminated with talimogene laherparepvec must observe institutional safety precautions.

Preparation to occur in biological safety cabinet per institutional guidelines.

Clean talimogene laherparepvec vial stopper with an alcohol swab.

Withdraw 1ml from each of 4 vials, using a sterile 18-26 gauge disposable needle, for a total volume of 4ml.

For additional information please refer to the talimogene laherparepvec pharmacy manual.

5.1.5 Return and Retention

The investigator is responsible for keeping accurate records of the clinical supplies received from Amgen, Inc. or designee, the amount dispensed to the subjects and the amount remaining at the conclusion of the trial.

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

5.1.6 Warnings and Precautions (talimogene laherparepvec)

Accidental Exposure

Accidental exposure may lead to transmission of herpetic infection. Healthcare providers who are immunocompromised or pregnant should not administer talimogene laherparepvec. Protective clothing and gloves should be worn during preparation and administration of talimogene laherparepvec.

Herpetic Infection

Herpetic infections have been reported in patients treated with talimogene laherparepvec. Healthcare providers exposed to talimogene laherparepvec are encouraged to report suspected herpetic infections as well. Disseminated herpetic infection may also occur in immunocompromised patients. Patients who develop suspicious herpes-like lesions should follow standard hygienic practices to prevent viral transmission. Suspected herpetic lesions should be reported to Amgen at 1-855-465-9442; patient or close contacts have the option of follow-up testing for further characterization of infection. Healthcare providers exposed to talimogene laherparepvec are encouraged to report the suspected herpetic infections to Amgen at 1-855-465-9442. Talimogene laherparepvec is sensitive to acyclovir.

Please see section 11.4 **Appendix D: Information sheet for caregivers, family members or other close contacts to clinical trial participants being given talimogene laherparepvec**.

Immune-mediated events

Talimogene laherparepvec may result in immune-mediated events including glomerulonephritis, vasculitis, pneumonitis, worsening of psoriasis, and vitiligo.

Common adverse events (≥ 25%) in talimogene laherparepvec-treated patients were fatigue, chills, pyrexia, nausea, influenza-like illness, and injection site pain.

Please refer to **the talimogene laherparepvec investigators brochure** for additional information on identified and potential risks.

5.2 Additional important Nivolumab (Opdivo®)

See the prescribing information for Opdivo® (Nivolumab) at http://packageinserts.bms.com/pi/pi_opdivo.pdf for more detailed information.

5.2.1 Description

Nivolumab injection drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10mg/10 mL. The vials supplied contain 100 mg. Nivolumab is a sterile, preservative-free, non-pyrogenic clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles for IV administration. Nivolumab will be administered as standard of care following the institutional guidelines.

5.2.2 Packaging and Labeling

Primary Packaging (Volume)/Label type: Carton of 5 or 10 vials
Secondary Packaging (Qty)/Label type: 10-cc Type 1 flint glass vials stoppered with butyl stoppers and sealed with aluminum seals.

5.2.3 Storage and Handling

Store nivolumab under refrigeration at 2^0C to 8^0C (36^0F-46^0F) in the original package until time of use. Protect from light and freezing. Do not shake the vial.

If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

5.2.4 Dose, Schedule and Administration

See section 4.3.2

Nivolumab will be given every two weeks at a dose of 240 mg to be administered as a 30 minute IV infusion.

Subjects may be dosed no less than 12 days from the previous dose of drug. There are no premedications recommended for nivolumab on the first cycle.

Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to institutional guidelines (See section 4.3.3).

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment.

5.2.5 Preparation

Follow institutional guidelines for Nivolumab preparation or see the nivolumab prescribing information for preparation instructions. Nivolumab Injection, 100 mg/10 mL (10 mg/mL) is to be administered as an IV infusion through a 0.2-micron

to 1.2-micron pore size, low-protein binding polyether sulfone (PES) membrane in-line filter at the protocol-specified dose. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 1 mg/mL. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

5.2.6 Stability

Nivolumab solution for injection can be stored after preparation at room temperature for no more than 4 hours. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion OR under refrigeration at 2^0C to 8^0C (36^0F-46^0F) for nor more than 24 hours from the time of infusion preparation.

5.2.7 Return and Retention of Nivolumab

Partially used and completely used vials will be destroyed per institutional guidelines.

5.2.8 Adverse Events Associated with Nivolumab

The adverse events listed below have been reported in patients receiving nivolumab. See section 4.3 for further instruction on the management adverse events associated with nivolumab therapy.

- Immune-mediated pneumonitis: Defined as requiring use of corticosteroids and no clear alternate etiology, including fatal cases have occurred with nivolumab treatment.
- Immune-mediated colitis: Defined as requiring use of corticosteroids and no clear alternate etiology, including fatal cases have occurred with nivolumab treatment.
- Immune-mediated hepatitis: Defined as requiring use of corticosteroids and no clear alternate etiology have occurred with nivolumab treatment.
- Immune-mediated endocrinopathies: Hypophysitis, adrenal insufficiency, hypo- and hyper-thyroidism, and type I diabetes mellitus have occurred with nivolumab treatment.
- Immune-mediated nephritis and renal dysfunction: Defined as renal dysfunction or ≥Grade 2 increased creatinine, requirement for corticosteroids, and no clear alternate etiology, can occur with nivolumab treatment.
- Immune-mediated rash: Severe rash (including rare cases of fatal toxic epidermal necrolysis) can occur with nivolumab treatment.
- Immune-mediated encephalitis: Withhold nivolumab in patients with new-onset moderate to severe neurologic signs or symptoms.
- Other immune-mediated adverse reactions: Monitor for as described in 4.3.2.

- Complications of allogeneic human stem cell transplant after nivolumab: Monitor for hyper acute graft-versus-host disease (GVHD). Transplant related mortality has occurred.
- Infusion reactions: Severe infusion reactions have been reported in <1.0% of patients in clinical trials of nivolumab. See section 4.3.3 for information on the management of nivolumab-related infusion reactions.

5.2.9 Use in Pregnancy

If a patient inadvertently becomes pregnant while on treatment with nivolumab, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated.

5.2.10 Use in Nursing Women

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

6.0 Evaluations and Assessments

6.1 Safety Run-in Cohort 1 (Talimogene Laherparepvec Only)

Assessments	Pre-Study[1]	Treatment Period[2] Cycle 1 is 3 weeks in length, subsequent cycles are Q2W							Follow up	
		Cycle 1 Day 1[1,2]	Cycle 1 Day 8	Cycle 2 Day 1	Cycle 2 Day 8	Cycle 3 Day 1	Cycle 4 Day 1	Cycle 5 - 9 Day 1	End of TXT[3]	Long Term FU[3]
Informed Consent	X									
HSV-1 antibody	X									
History[4]	X	X	X	X	X	X	X	X	X	X
Physical exam[4]	X	X	X	X	X	X	X	X	X	
Performance Status	X	X	X	X	X	X	X	X	X	
EKG	X						X			
Troponin	X						X			
Chest X-ray	X	As needed and/or after three consecutive drainages with ≤50cc drainage (every other day drainages) of pleural fluid drainage accompanied by patient-defined improvement in symptoms (cough, chest pain and/or dyspnea).							X	
Tumor measurement[5]	X							X[5]	X[5]	X
Pregnancy test[1]	X									
Hematology[6]	X[6]	X	X	X	X	X	X	X	X	
Serum chemistries[6]	X	X	X	X	X	X	X	X	X	
Liver function tests[6]	X	X	X	X	X	X	X	X	X	
Coagulation[7]	X									
Toxicity Assessment	X	X	X	X	X	X	X	X	X	X
Concomitant Meds	X	X	X	X	X	X	X	X	X	
talimogene laherparepvec IP Q3W 10^6 PFU		X								
talimogene laherparepvec IP Q2W 10^8 PFU				X		X	X	X		

Assessments	**Pre-Study[1]**	**Treatment Period[2] Cycle 1 is 3 weeks in length, subsequent cycles are Q2W**							**Follow up**	
		Cycle 1 Day 1[1,2]	**Cycle 1 Day 8**	**Cycle 2 Day 1**	**Cycle 2 Day 8**	**Cycle 3 Day 1**	**Cycle 4 Day 1**	**Cycle 5 - 9 Day 1**	**End of TXT[3]**	**Long Term FU[3]**
Patient Diary[8]		X	X	X	X	X	X	X	X	
Blood / urine / pleura samples to assess viral shedding		X[9]	X[9]	X[9]	X[9]	X[9]	X[9]		X[9]	
Blood sample for correlative studies[10]		X		X			X		X	
Tumor biopsy	X[11]									
Collection of pleural drainage[12]		X		X					X	
Buccal Swab	X[14]	X[15]								
Modified Borg[13]		X		X			X		X	
Survival analysis										X

Key to Time and Events Table Footnotes

1. Radiological assessments, EKG and physical exam may be performed up to 4 weeks prior to day 1 of treatment. Other evaluations except for pregnancy must be performed within 2 weeks prior to Cycle 1 Day 1 of treatment. Serum B-HCG must be performed within 72 hours prior to first dose of study medication for women of child-bearing potential. Screening labs performed within 72 hours prior to Cycle 1 Day 1 do not need to be repeated on C1D1.

2. The first treatment cycle with talimogene laherparepvec is 3 weeks (21 days) in length to allow for seroconversion (See Schema in 4.1). Subsequent treatment cycles are to be repeated every 2 weeks (14 days) X 8 cycles or until progression, whichever occurs first. **A window of +/- 2 days applies to all study visits within the treatment period.**

3. The end of treatment/safety follow up visit should only occur when patients permanently stop study treatment and should be performed 30 days (+/-7 days) after the last dose of study medication. Patients who have an ongoing ≥grade 2 or serious AE (SAE) at this visit will continue to be followed until the event is resolved or deemed irreversible by the investigator. Patients stopping talimogene laherparepvec should be monitored for at least 30 days for emerging AEs after discontinuing the drug. After two years of follow-up per standard of care (Q3 months +/- 15 days) as outlined in the time and events table, subsequent follow up will be by phone contact or via medical records to document disease progression and survival information until death (Q3 months +/- 15 days).

4. Complete history at baseline only (to include smoking history), thereafter focused history on symptoms/toxicity; physical exam to include height (baseline only), examination of the skin, weight, pulse oximetry, and vital signs.

5. Tumor imaging should remain consistent throughout study and performed at baseline, just prior to D1 of cycle 5, at progression or the end of treatment (i.e. completion of cycle 9), and should include those thought by investigator to best capture status of disease. Examples include PET, contrasted computed tomography (CT) of the chest, abdomen and pelvis, and bone scan. Imaging following completion of study procedures should be per standard of care for the relevant disease sate.

6. Hematology: CBC with differential and platelet count; Liver function tests: total bilirubin, direct bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase, direct bilirubin if indicated, at screening only. Serum chemistry: potassium, sodium, calcium, creatinine, chloride, glucose, magnesium, phosphorus, BUN, albumin, uric acid, and total protein.

7. Coagulation: PT or INR and PTT or aPTT

8. Patient drainage diary (See Appendix E in Section 11.5)

9. Collect urine, pleura and 5 mL of blood (lavender top EDTA tube) at each time point denoted below. Additional details on sample collection provided in the study laboratory manual.
    - C1D1: pre-dose, 1 hr post dose, 4 hrs post dose and 6 hrs post dose samples
    - Collect predose samples on C1D8/C2D1/C2D8/C3D1/C4D1 and at end of treatment

10. Blood samples will be collected for correlative studies (at pretreatment, 3 weeks post treatment, 9 weeks post treatment, and end of treatment according to lab manual.

11. Tumor biopsy will be collected for correlative studies. All subjects in this study will have had pleural catheter placed as standard of care, which will allow for fresh biopsy collection. If for some reason fresh biopsy cannot be collected, archival tumor will be accepted.

12. If feasible, Pleural fluid will be collected for correlative studies at the following time points: pre treatment, 3 weeks post treatment, 9 weeks post treatment, and end of treatment, according to the lab manual.

13. Modified Borg Rating of Perceived Dyspnea (MBS) will be used to assess level of exertion (Provided in 11.6 Appendix F: Borg Scale).

14. Buccal swab for matched normal genomic DNA
15. Repeat if insufficient sequencing.

6.2 Safety Run-in Cohort 2 and expansion (Combination)

Assessments	Pre-Study[1]	Treatment Period[2] Cycle 1 is 3 weeks in length, subsequent cycles are Q2W							Follow up	
		Cycle 1 Day 1[1]	Cycle 1 Day 8	Cycle 2 Day 1	Cycle 2 Day 8[3]	Cycle 3 Day 1	Cycle 4 Day 1	C5 – 9N Day 1	End of TXT[4]	Long Term FU[4]
Informed Consent	X									
HSV-1 antibody	X									
History[5]	X									
Physical exam[5]	X	X	X	X	X	X	X	X	X	
Performance Status	X	X	X	X	X	X	X	X	X	
EKG	X						X			
Troponin	X						X			
Chest x-ray	X	As needed and within 21 days of final drainage ≤ 50 mL							X	
Tumor measurement[6]	X							X[6]	X[6]	X
Pregnancy test[1]	X									
Hematology[7]	X	X	X	X	X	X	X	X	X	
Serum chemistries[7]	X	X	X	X	X	X	X	X	X	
Liver function tests[7]	X	X	X	X	X	X	X	X	X	
Coagulation[8]	X									
Toxicity Assessment	X	X	X	X	X	X	X	X	X	X
Concomitant Meds	X	X	X	X	X	X	X	X	X	
talimogene laherparepvec IP Q3W 10^6 PFU		X								
talimogene laherparepvec IP Q2W 10^8 PFU[9]				X		X	X	X		
Nivolumab IV Q2W		X		X		X	X	X		
Patient diary[10]		X	X	X	X	X	X	X	X	

Assessements	**Pre-Study[1]**	**Treatment Period[2] Cycle 1 is 3 weeks in length, subsequent cycles are Q2W**							**Follow up**	
		Cycle 1 Day 1[1]	**Cycle 1 Day 8**	**Cycle 2 Day 1**	**Cycle 2 Day 8[3]**	**Cycle 3 Day 1**	**Cycle 4 Day 1**	**C5 – 9N Day 1**	**End of TXT[4]**	**Long Term FU[4]**
Blood/urine/pleura samples to assess viral shedding		X[11]	X[11]	X[11]	X[11]	X[11]	X[11]		X[11]	
Blood sample for correlative studies[12]		X		X			X		X	
Tumor biopsy[13]	X									
Collection of pleural drainage[14]		X		X			X		X	
Buccal Swab	X[16]	X[17]								
Modified Borg[15]		X		X			X		X	
Survival analysis										X

Key to Time and Events Table Footnotes

1. Radiological assessments, EKG and physical exam may be performed up to 4 weeks prior to day 1 of treatment. Other evaluations except for pregnancy must be performed within 2 weeks prior to Cycle 1 Day 1 of treatment. Serum B-HCG must be performed within 72 hours prior to first dose of study medication for women of child-bearing potential. Screening labs performed within 72 hours prior to Cycle 1 Day 1 do not need to be repeated on C1D1.

2. The first treatment cycle with talimogene laherparepvec is 3 weeks in length (21 days) to allow for seroconversion (See Schema in 4.1). Subsequent treatment cycles are to be repeated every 2 weeks (14 days) X 8 cycles or until progression, whichever occurs first. **A window of +/- 2 days applies to all study visits within the treatment period**.

3. **Visit may be deemed optional at the behest of the investigator.**

4. The end of treatment/safety follow up visit should only occur when patients permanently stop study treatment and should be performed 30 days (+/-7 days) after the last dose of study medication. Patients who have an ongoing ≥grade 2 or serious AE (SAE) at this visit will continue to be followed until the event is resolved or deemed irreversible by the investigator. Patients stopping nivolumab should be monitored for at least 100 days after discontinuing the drug for the emergence of SAEs. After two years of follow-up per standard of care (**Q3 months +/- 15 days**) as outlined in the time and events table, subsequent follow up will be by phone contact or via medical records to document disease progression and survival information until death (Q3 months +/- 15 days).

5. Complete history at baseline only (to include smoking history); thereafter focused history on symptoms/toxicity physical exam to include height (baseline only), examination of the skin, weight, pulse oximetry, and vital signs.

6. Tumor imaging should remain consistent throughout study, and should include those thought by investigator to best capture status of disease. Examples include PET, contrasted computed tomography (CT) of the chest, abdomen and pelvis, and bone scan. During the treatment period scans should occur prior to Cycle 5 Day 1 and every 4 cycles after that until progression. Imaging following completion of study procedures should be per standard of care for the relevant disease state.

7. Hematology: CBC with differential and platelet count; Liver function tests: total bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase; direct bilirubin if indicated, at screening only. Serum chemistry: potassium, sodium, calcium, creatinine, chloride, glucose, magnesium, phosphorus, BUN, albumin, uric acid, and total protein.

8. Coagulation: PT or INR and PTT or aPTT

9. Talimogene Laherparepvec administration only through Cycle 9.

10. Patient drainage diary (See Appendix E in Section 11.5)

11. Collect urine, pleura and 5 mL of blood (lavender top EDTA tube) at each time point denoted below. Additional details on sample collection provided in the study laboratory manual
    - C1D1: predose, 1 hr post dose, 4 hrs post dose and 6 hrs post dose samples
    - Collect predose samples on C1D8/C2D1/C2D8/C3D1/C4D1 and at end of treatment

12. Blood samples will be collected for correlative studies (3x 8mLs whole blood in ACD tubes will be collected to evaluate for clonally restricted circulating B and T cells).

13. Tumor biopsy will be collected for correlative studies. All subjects in this study will have had pleural catheter placed as standard of care, which will allow for fresh biopsy collection. If for some reason fresh biopsy cannot be collected, archival tumor will be accepted.

14. Pleural fluid will be collected studies at the following time points: pre treatment, 3 weeks post treatment, 9 weeks post treatment, and end of treatment, separated by the LCCC Immune Monitoring and Genomics Facility (IMGF) into two portions: one portion (prioritized) will be used for correlativestudies and the second portion will be distributed to CTU lab for long term storage.

15. Modified Borg Rating of Perceived Dyspnea (MBS) will be used to assess level of exertion **(Provided in 11.6** Appendix F: Borg Scale).

16. Buccal swab for matched normal genomic DNA

17. Repeat if insufficient sequencing.

6.3 Pre-Study Assessments for Safety Run in Cohorts and Phase II (Tables 6.1 and 6.2)

Screening evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Scans for tumor evaluation must be done within 4 weeks prior to the start of therapy. (**Note**: Hematology and other lab parameters that are ≤ grade 2 BUT still meet criteria for study entry are allowed. Furthermore, changes in laboratory parameters during the study should not be considered adverse events unless they meet criteria for dose modification(s) of study medication outlined by the protocol and/or worsen from baseline during therapy). Pre-study assessments include:

Complete medical history (including smoking history) and physical examination (including skin exam, height, and weight)
ECOG Performance Status (see appendix A)
Laboratory evaluations:

- CBC with differential
- Serum chemistries (potassium, sodium, calcium, creatinine, chloride, glucose, magnesium, phosphorus, BUN, albumin, uric acid, and total protein)
- Liver function tests (total bilirubin, direct bilirubin if indicated, alkaline phosphatase, AST, ALT)
- Troponin
- Serum pregnancy test in women of childbearing potential (Note: pregnancy test to be done within 72 hours of day 1 of treatment)
- Coagulation (PT/INR)
- HSV-1 antibody test
- Blood samples collected for correlative studies

EKG
Chest x-ray after thoracentesis (baseline)
Concomitant medication(s): All concomitant medications will be recorded.
Tumor evaluation: CT or MRI scan of the neck, results from physical examination head and neck, and chest imaging (x-ray or CT scan at discretion of physician)

Tumor biopsy: All subjects will have catheter placed per standard of care, therefore fresh biopsy should be easily accessible. If fresh biopsy is unavailable, archival will be accepted.
Toxicity evaluation: Use NCI CTCAEv5.0 for notation of any baseline toxicity
Modified Borg Scale of Perceived Dyspnea (Provided in 11.6 Appendix F: Borg Scale): Scale ranging from 0 (no dyspnea) to 10, which evaluates perceived level of shortness of breath.

6.4 Study Treatment Assessments (+/- 2 days)

6.4.1 Cycle 1/Day 1 Safety Run-in/Phase II expansion (6.1, 6.2)

Physical examination (including weight and symptom directed medical history
ECOG Performance Status (see appendix A)
Laboratory evaluations (to be obtained prior to treatment):

- CBC with differential
- Serum chemistries (potassium, sodium, calcium, creatinine, chloride, glucose, magnesium, phosphorus, BUN, albumin, uric acid, and total protein)
- Liver function tests (total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT)
- Serial sampling of blood/urine/pleura to assess viral shedding (pre-dose & 1hr, 4hr and 6hr post dose samples) following IP talimogene laherparepvec. Pleural fluid will be separated by the LCCC Immune Monitoring and Genomics Facility (IMGF) into two portions: one portion will be used for correlative studies, and the second portion will be distributed to the CTU laboratory for long term storage at -80°C for possible assessment of viral shedding for up to two years after study completion. If insufficient amount of pleural fluid is collected, priority will be given to a sample used for correlative studies.
- Blood samples collected for correlative studies

Concomitant medication(s): All concomitant medications will be recorded.
Toxicity evaluation: Use NCI CTCAE v5.0
Collection of Pleural drainage: prior to talimogene laherparepvec administration, if feasible
For Safety run-in cohort 1 (6.1): Administer premedications, followed by talimogene laherparepvec only 4 $x10^6$ pfu via pleurX catheter
For Safety run-in cohort 2 and Phase II expansion (6.2): Administer premedications , followed by talimogene laherparepvec 4 $x10^6$ pfu via pleurX catheter + 240 mg nivolumab IV
Modified Borg Scale of Perceived Dyspnea (Provided in 11.6 Appendix F: Borg Scale): Scale ranging from 0 to 10, which evaluates perceived level of shortness of breath.
Patient Catheter drainage diary
Chest x-ray within 21 days of the final drainage of ≤ 50 mL, if applicable.

6.4.2 Cycles 1 & 2/Day 8 Safety Run-in/Phase II expansion (6.1, 6.2)

Physical examination (including weight)
ECOG Performance Status (see appendix A)
Laboratory evaluations (to be obtained prior to treatment):

- CBC with differential
- Serum chemistries (potassium, sodium, calcium, creatinine, chloride, glucose, magnesium, phosphorus, BUN, albumin, uric acid, and total protein)
- Liver function tests (total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT)
- Blood/urine/pleura samples to assess viral shedding (pre-dose). Samples will be frozen and stored for future research for up to two years after study completion.

Concomitant medication(s): All concomitant medications will be recorded.
Toxicity evaluation: Use NCI CTCAEv5.0
Review patient diaries
Chest x-ray as needed clinically and/or after three consecutive drainages with ≤50cc drainage (every other day drainages) of pleural fluid drainage accompanied by patient-defined improvement in symptoms (cough, chest pain and/or dyspnea).

For Phase II expansion only: Once safety is established for the combination, the Day 8 visit during cycles 1 and 2 may be deemed optional and not required at the behest of the investigator.

6.4.3 Cycle 2 Day 1 Safety Run-in/Phase II expansion (6.1, 6.2)

Physical examination (including weight and symptom directed medical history)
ECOG Performance Status (see appendix A)
Laboratory evaluations (to be obtained prior to treatment):

- CBC with differential
- Serum chemistries (potassium, sodium, calcium, creatinine, chloride, glucose, magnesium, phosphorus, BUN, albumin, uric acid, and total protein)
- Liver function tests (total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT)
- Blood/urine/pleura samples to assess viral shedding (pre-dose). Pleural fluid will be separated by the LCCC Immune Monitoring and Genomics Facility (IMGF) into two portions: one portion will be used for correlative studies, and the second portion will be distributed to the CTU laboratory for long term storage at -80°C for possible assessment of viral shedding for up to two years after study completion. If insufficient amount of pleural fluid is collected, priority will be given to a sample used for correlative studies.
- Blood samples collected for correlative studies

Concomitant medication(s): All concomitant medications will be recorded.
Toxicity evaluation: Use NCI CTCAEv5.0

Collection of Pleural drainage: prior to talimogene laherparepvec administration
Modified Borg Scale of Perceived Dyspnea (Provided in 11.6 Appendix F: Borg Scale): Scale ranging from 0 to 10, which evaluates perceived level of shortness of breath.
For Safety run-in cohort 1 (6.1): (premeds) Administer talimogene laherparepvec only 4 x10^8 pfu via pleurX catheter
For Safety run-in cohort 2 and Phase II expansion (6.2): (premeds) Administer talimogene laherparepvec 4 x10^8 pfu via pleurX catheter + 240 mg nivolumab IV
Patient diaries
Chest x-ray as needed and/or after three consecutive drainages with ≤50cc drainage (every other day drainages) of pleural fluid drainage accompanied by patient-defined improvement in symptoms (cough, chest pain and/or dyspnea).

6.4.4 Day 1/Cycle 3 Safety Run-in/Phase II expansion (6.1, 6.2)

Physical examination (including weight and symptom directed medical history)
ECOG Performance Status (see appendix A)
Laboratory evaluations (to be obtained prior to treatment):

- CBC with differential
- Serum chemistries (potassium, sodium, calcium, creatinine, chloride, glucose, magnesium, phosphorus, BUN, albumin, uric acid, and total protein)
- Liver function tests (total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT)
- Blood/urine/pleura samples to assess viral shedding (pre-dose). Samples will be frozen and stored for future research for up to two years after study completion.

Concomitant medication(s): All concomitant medications will be recorded.
Toxicity evaluation: Use NCI CTCAEv5.0
Patient diaries
Chest x-ray as needed and/or after three consecutive drainages with ≤50cc drainage (every other day drainages) of pleural fluid drainage accompanied by patient-defined improvement in symptoms (cough, chest pain and/or dyspnea).

For Safety run-in cohort 1 (6.1): Administer talimogene laherparepvec only 4 x10^8 pfu via pleurX catheter
For Safety run-in cohort 2 and Phase II expansion (6.2 and 6.3): (premeds) Administer talimogene laherparepvec 4 x10^8 pfu via pleurX catheter + 240 mg nivolumab IV

6.4.5 Day 1/Cycle 4 Safety Run-in/Phase II expansion (6.1, 6.2)

Physical examination (including weight and symptom directed medical history)
ECOG Performance Status (see Section 11.1)
Laboratory evaluations (to be obtained prior to treatment):

- CBC with differential

- Serum chemistries (potassium, sodium, calcium, creatinine, chloride, glucose, magnesium, phosphorus, BUN, albumin, uric acid, and total protein)
- Troponin
- Liver function tests (total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT)
- Blood/urine/pleura samples to assess viral shedding (pre-dose). Pleural fluid will be separated by the LCCC Immune Monitoring and Genomics Facility (IMGF) into two portions: one portion will be used for correlative studies, and the second portion will be distributed to the CTU laboratory for long term storage at -80°C for possible assessment of viral shedding for up to two years after study completion. If insufficient amount of pleural fluid is collected, priority will be given to a sample used for correlative studies.
- Blood samples collected for correlative studies

EKG

Concomitant medication(s): All concomitant medications will be recorded.

Toxicity evaluation: Use NCI CTCAEv5.0

Collection of Pleural drainage: prior to talimogene laherparepvec administration

Modified Borg Scale of Perceived Dyspnea (Provided in 11.6 Appendix F: Borg Scale): Scale ranging from 0 to 10, which evaluates perceived level of shortness of breath.

Patient diaries

Chest x-ray as needed and/or after three consecutive drainages with ≤50cc drainage (every other day drainages) of pleural fluid drainage accompanied by patient-defined improvement in symptoms (cough, chest pain and/or dyspnea).

For Safety run-in cohort 1 (6.1): (premeds) Administer talimogene laherparepvec only 4 x10^8 pfu via pleurX catheter

For Safety run-in cohort 2 and Phase II expansion (6.2): (premeds) Administer talimogene laherparepvec 4 x10^8 pfu via pleurX catheter + 240 mg nivolumab IV

6.4.6 Day 1/Cycle 5-N Safety Run-in/Phase II expansion (6.1, 6.2)

Physical examination (including weight and pulse oximetry)

ECOG Performance Status (see appendix A)

Laboratory evaluations (to be obtained prior to treatment):

- CBC with differential
- Serum chemistries (potassium, sodium, calcium, creatinine, chloride, glucose, magnesium, phosphorus, BUN, albumin, uric acid, and total protein)
- Liver function tests (total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT)

Concomitant medication(s): All concomitant medications will be recorded.

Toxicity evaluation: Use NCI CTCAEv5.0

Tumor evaluation: CT or MRI scan of the neck, results from physical examination head and neck, and chest imaging (x-ray or CT scan at discretion of physician).

Scans are to be performed prior to Cycle 5 Day 1 and every 4 cycles after until disease progression.

For Safety run-in cohort 1 (6.1): Administer talimogene laherparepvec only 4 x10^8 pfu via pleurX catheter per standard of care of related disease state

For Safety run-in cohort 2 and Phase II expansion (6.2): Administer talimogene laherparepvec 4 x10^8 pfu via pleurX catheter + 240 mg nivolumab IV
Patient diaries
Chest x-ray as needed and/or after three consecutive drainages with ≤50cc drainage (every other day drainages) of pleural fluid drainage accompanied by patient-defined improvement in symptoms (cough, chest pain and/or dyspnea).

6.5 Post-Treatment/Follow-up Assessments

6.5.1 End of Treatment Safety Run-in/Phase II expansion (6.1, 6.2) (+/- 7 days)

Physical examination (including weight and symptom directed medical history)
ECOG Performance Status (see appendix A)
Laboratory evaluations:

- CBC with differential
- Serum chemistries (potassium, sodium, calcium, creatinine, chloride, glucose, magnesium, phosphorus, BUN, albumin, uric acid, and total protein)
- Liver function tests (total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT)
- Blood/urine/pleura samples to assess viral shedding. Pleural fluid will be separated by the LCCC Immune Monitoring and Genomics Facility (IMGF) into two portions: one portion will be used for correlative studies, and the second portion will be distributed to the CTU laboratory for long term storage at -80°C for possible assessment of viral shedding for up to two years after study completion. If insufficient amount of pleural fluid is collected, priority will be given to a sample used for correlative studies.
- Blood samples collected for correlative studies

Concomitant medication(s): All concomitant medications will be recorded.
Toxicity evaluation: Use NCI CTCAEv5.0
Collection of Pleural drainage if feasible
Modified Borg Scale of Perceived Dyspnea (Provided in 11.6 Appendix F: Borg Scale): Scale ranging from 0 to 10, which evaluates perceived level of shortness of breath.
Patient diaries
Chest x-ray as needed and/or after three consecutive drainages with ≤50cc drainage (every other day drainages) of pleural fluid drainage accompanied by patient-defined improvement in symptoms (cough, chest pain and/or dyspnea).

The end of treatment/safety follow up visit should only occur when patients permanently stop study treatment and should be performed 30 days (+/-7 days) after the last dose of study medication. Patients who have on ongoing ≥grade 2 or serious AE (SAE) at this visit will continue to be followed until the event is resolved or deemed irreversible by the investigator.

Subjects discontinuing nivolumab should be monitored for at least 100 days after discontinuing the drug for the emergence of SAEs.

6.5.2 Subsequent Follow-up

Subjects withdrawn from study therapy will be followed every 3 months (+/- 15 days) per standard of care. These visits will be limited to history of any subsequent cancer treatments, an assessment of any SAE's considered to be possibly or probably related to study treatment until resolution, and survival status. After two years of follow-up as described in the time and events tables, subsequent follow-up will be per standard of care and subjects will be contacted by phone or via medical records for progression and survival information (every 3 months +/- 15 days) until death.

6.6 Correlative Studies Procedures

Peripheral blood, pleural fluid, and tumor biopsy samples will be collected as a part of this study, according to the time and events table above. Tumor biopsies will be classified as for research purposes only. Peripheral blood will be processed according to TPF standard protocol for generating viably frozen PBMC fractions. Pleural fluid samples will be processed fresh; half of each sample will be allocated for flow cytometry studies and half for RNA sequencing.

Pleural fluid and tumor biopsy samples will undergo RNA extraction and preparation of next generation sequencing libraries for RNA sequencing and T cell receptor repertoire sequencing according to Immune Monitoring and Immunogenomics Facility (IMGF) protocols. The RNA sequencing studies are classified as genetic research and will include information regarding somatic mutations. This will be included in the informed consent documentation supporting this trial.

Handling of Biospecimens Collected for Correlative Research

Biospecimens collected for this study will be stored in the Lineberger Comprehensive Cancer Center (LCCC) Tissue Procurement Facility (TPF), or if needed, in a secure off-site storage facility. All biospecimen samples will be obtained in accordance with procedures outlined in the LCCC 1626 Study Laboratory Manual and stored in containers with controlled access. Each sample will be assigned a unique code number and no identifiable personal health information (PHI) will be on the specimen label. Information about the patient's disease will be linked to the specimens stored in the repository database. TPF-associated research staff, LCCC Bioinformatics staff who support the TPF database and the LCCC Data Warehouse, and researchers with IRB-approval for access to

PHI for each subject in this study will be able to link specimens to relevant medical information. Some results from laboratory analyses that occurred during the patient's participation in the clinical study may also be included. This information may be important for understanding how the patient's cancer developed and responded to treatment.

Storage Time:

- The biospecimen will be used first and foremost for research purposes outlined within the confines of this protocol. Samples will be discarded/destroyed after relevant data are collected for this study, unless consent was obtained from the patient to use tissue for other research purposes (e.g., TPF consent form was signed by the patient). In this circumstance, there is no time limit on how long biospecimens may be stored.
- The investigator must agree to abide by policies and procedures of the TPF facility and sign a letter of research agreement for ethical and appropriate conduct of their research that utilizes specimens obtained from the TPF facility (e.g., Use of leftover specimens will require a protocol outlining the research plan for biospecimen use).

Compliance Statement

Biospecimen collection for this study will be conducted in full accordance to all applicable University of North Carolina (UNC) Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, and the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. Any episode of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent (unless a waiver is granted), and will report unexpected problems in accordance with The UNC IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

6.7 Assessment of Safety

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed periodically for the development of any toxicity according to the Time and Events tables. Toxicity will be assessed according to the NCI CTCAE v5.0.

6.8 Evaluation of Response by irRECIST [62] per Bohnsack et al.

New measurable lesions in irRECIST:

New measurable lesions will not necessarily constitute PD or preclude partial response (PR). Rather, the difference between the current size of a measurable

lesions and its size prior to meeting criteria for measurability will be added to the sum of tumor measurements.

Definition of Response Using irRECIST

irComplete Response (irCR): Complete disappearance of all lesions (whether measurable or not) and no new lesions. Lymph nodes must decrease to <10mm in short axis. Confirmation of a response is not mandatory. It is the judgment of the investigator whether a nonmeasurable radiographic nodule is likely cancerous; only nodules felt likely cancerous will preclude the judgement of irCR.

- irPartial Response (irPR): Decrease in tumor burden ≥ 30%, in total measured tumor burden relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions

- irNon CR/Non-PD (irNN): No target disease was identified at baseline and at follow up the patient fails to meet criteria for irCR or irPD.

- irStable Disease (irSD): Does not meet criteria for irCR or irPR, in the absence of irPD.

- irProgressive Disease (irPD): At least 20% and minimum 5 mm absolute increase in total measured tumor burden compared to nadir, or irPD for non-target or new on-measureable lesions. Confirmation of progression is recommended minimum of 4 weeks after the first irPD assessment.

- Nonprogressive disease: Measurable disease is not required for this study. Patients with CR at the time of study entry or otherwise nonmeasurable disease will be assessed for progression. In the event of PD, this should be noted. In the absence of meeting criteria for progression, nonprogressive disease should be coded (NPD).

Immune-related Best Overall Response (irBOR):

IrBOR is the best response observed during the relevant time period. Of note, when total tumor burden increases and the patient is maintained on therapy, and tumor then shrinks (pseudo-progression) the second measurement will be utilized.

Designation of pseudo-progression:

The phenomenon of pseudo-progression is of particular interest in this trial. For the purpose of this trial, pseudo-progression will be defined as any ≥ 10% increase in tumor burden followed by a ≥ 10% decrease in tumor burden prior to change in therapy. Such occurrences will be noted for the purpose of exploratory hypothesis-generating analyses.

7.0 ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a drug) in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy.

From the time of treatment 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 7.3. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

7.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the drug is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study drug exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be

needed before the sponsor could determine that there is *reasonable possibility* that the drug caused the event.

- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug treatment group than in a concurrent or historical control group

7.1.3 Unexpected AE or SAR

An AE or SAR is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure (IB) for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious AE or SAR

An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.
- Potential drug induced liver injury (DILI) is also considered an important medical event.
- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.
- Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional

therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

Pregnancy that occurs during the study must also be reported as an SAE.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the BMS and Amgen in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by BMS for collection purposes.

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

7.2 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue through the 100 day follow-up period after nivolumab treatment is discontinued. Subjects should be followed for AEs for at least 30 days after talimogene laherparepvec is discontinued.

Collected information should be recorded in the Case Report Forms (CRF) for that patient. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug.

7.3 SAEs or Serious SARs

7.3.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout).

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin from day 1 of study treatment and continue at least through the 100 day follow-up period after treatment is discontinued. Ultimately, the event should be followed until resolution of symptoms or the investigator determines that symptoms have improved to the fullest extent possible.

7.3.2 Documentation and Notification

SAEs or Serious SARs must be recorded in the SAE console within Oncore™ for that patient within 24 hours of learning of its occurrence.

7.3.3 Reporting

7.3.3.1 IRB Reporting Requirements:

The UNC-IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting

system (see section 9.5.3) within 7 days of the Investigator becoming aware of the problem.

7.3.3.2 Pregnancy

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 subject (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 subject 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 suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study or within 30 days of the subject's last dose of talimogene laherparepvec or within the period stipulated for continued contraceptive use for WOCBP (5 months) and sexually active men (7 months) after the subject's last dose of nivolumab should be recorded as SAEs. The patient is to be discontinued immediately from the study for a pregnancy event.

The Investigator will follow the female subject until completion of the pregnancy, and must document the outcome of the pregnancy (either normal or abnormal outcome) and report the condition of the fetus or newborn to the UNC study coordinator. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE.

7.3.3.3 Laboratory Test Abnormalities

The following laboratory abnormalities should be documented and reported appropriately as AEs:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

7.3.3.4 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

7.3.3.5 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

7.3.3.6 Amgen Reporting Requirements:

Please refer to the table below regarding policy for reporting SUSARs, and other safety related data to Amgen.

Expedited Reporting Requirements for Interventional Studies

Safety Data	Timeframe for Submission to Amgen
Suspected Unexpected Serious Adverse Reaction (SUSARs)	Individual reports sent to Amgen at time of expedited reporting to the IRB and/or FDA
Serious Adverse Events (SAEs) (related)	Individual reports sent to Amgen at time of expedited reporting to IRB and/or FDA
Pregnancy/Lactation	Individual reports sent within 10 days of Sponsor/Investigator awareness (Use Amgen template forms provided for the study to report pregnancy or lactation events).

Individual reports should be faxed to 1-888-814-8653 or scanned and sent via email to svc-ags-in-us@amgen.com.

Aggregate reports should be submitted via email to the non-Amgen sponsored Clinical Research (NASCR) manager accompanied by the Aggregate Safety Reporting fax transmittal form for Investigator Sponsored Studies provided for the study.

Please refer to the ICH Guidelines E2A for safety related definitions and terminology:
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf

7.3.3.7 Suspected Herpetic Events

Suspected herpetic events must be reported to Amgen within 24 hours of awareness. Reporting is required for: (1) suspected herpetic events in treated patients; (2) suspected herpetic events in at risk health care professionals with direct or indirect exposure and 3) suspected herpetic events in treated patient's close contacts.

In addition to reporting these events, suspected herpetic lesions should be swabbed and submitted for quantitative polymerase chain reaction testing for the detection of talimogene laherparepvec. Samples should be collected using appropriate technique and a flocked swab from site supplies. This test is likely to

be more reliable if performed within **the first three days of symptom appearance**. Amgen does not require quantitative polymerase chain reaction or other testing for wild type herpes simplex virus-1. See section below on reporting process for health care providers which should be followed if herpetic lesions are suspected.

Reporting Process for Treated Patients:

- Any suspected herpetic lesion should be reported to Amgen at 1-855-465-9442 or 1-855-IMLYGIC, evaluated by the sponsor/investigator and swabbed for quantitative polymerase chain reaction testing
- Once an initial report has been made, additional materials will be provided, including reporting forms and supplies needed for shipment of swab samples. Amgen will require patient consent for quantitative polymerase chain reaction testing, which must be obtained prior to swabbing.

Reporting process for health care providers and close contacts:

- Sponsor investigator should advise any health care providers and/or close contacts with suspected herpetic lesions to contact their personal physician to facilitate reporting to Amgen. Suspected herpetic lesions should be reported by the personal physician or exposed individual to Amgen at 1-855-465-9442. Once an initial report has been made, additional materials will be provided, including reporting forms and supplies needed for shipment of swab samples. Amgen will require patient consent for quantitative polymerase chain reaction testing, which must be obtained prior to swabbing.

7.3.3.8 FDA Expedited Reporting requirements for studies conducted under an IND:

A sponsor must report any suspected adverse reaction that is both serious and unexpected to the FDA. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event. Refer to Section 7.1.2 for the definition of SAR.

The sponsor must submit each IND safety report on FDA Form 3500A.

Timing

FDA must be notified of potential serious risks within 15 calendar days after the sponsor determines the event requires reporting. FDA must be notified of unexpected fatal or life-threatening suspected adverse reactions as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information. If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable is reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

Follow-up
The sponsor must promptly investigate all safety information it receives. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available.

Notification of Investigators
The sponsor must notify all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

Process
If the sponsor deems that an event is both a serious SAR AND unexpected, it must also (in addition to Oncore™) be recorded on the MedWatch Form 3500A as per 21 CFR 312.32. Unexpected adverse events or adverse reaction refers to an event or reaction that is not listed in the investigator's brochure or is not listed at the specificity or severity that has been observed; or if an investigator's brochure is not required or available, is not consistent with the risk information described in the general investigation plan or elsewhere in the current IND application.

The FDA must be notified or any unexpected or life-threatening suspected adverse reactions as soon as possible, but no later than 7 calendar days of learning of the event.

Additional Reporting Requirements
The following additional items must be reported via IND safety report:

- *Findings from other studies.* The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk to humans exposed to the drug.
- *Findings from animal or in vitro testing.* The sponsor must report any findings from animal or *in vitro* testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity t or near the expected human exposure.
- *Increased rate of occurrence of serious suspected adverse reactions.*

Additional Guidance
Please refer to 21CFR312.32 and "Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies" for additional information and reporting requirements. All IND Safety Reports will be submitted in accordance with these regulations/guidances.

7.3.3.9 Institutional Biosafety Committee (IBC)

In addition to the local IRB, any qualifying serious adverse events (SAEs) must be reported to the Institutional Biosafety Committee (IBC). The IBC is responsible for reviewing recombinant DNA research conducted at or sponsored by the institution for compliance with NIH Guidelines as specified in Section III, Experiments covered by the NIH Guidelines and approving those research projects that are found to conform with the NIH Guidelines. As such, the IBC is charged with ensuring compliance with all surveillance, data reporting and adverse event reporting requirements set forth in the NIH Guidelines.

7.4 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of patient safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC).

Meetings/teleconferences will be held at a frequency dependent on study accrual, and in consultation with the study Biostatistician. These meetings will include the investigators as well as study coordinators, data coordinators, regulatory associates, clinical data management associates, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight (Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

The UNC LCCC Data and Safety Monitoring Committee (DSMC) will review the study on a regular (quarterly to annually) basis, with the frequency of review based on risk and complexity as determined by the UNC Protocol Review Committee. The principal investigator will be responsible for submitting the following information for review: 1) safety and accrual data including the number of patients treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4) summaries of team meetings that have occurred since the last report. Findings of the DSMC review will be disseminated by memo to the principal investigator, PRC, and the UNC IRB.

8.0 STATISTICAL CONSIDERATIONS

8.1 Study Design/Study Endpoints

A 3 + 3 dose escalation scheme will be used for Dose Level 1 safety run-in followed by Dose Level 2 evaluation for the primary endpoint. In Phase I, patients will be assigned in cohorts of 3, starting with Dose Level 1. The acceptable dose will be defined as the highest dose at which ≤1 out of 6 patients have experienced a dose limiting toxicity (DLT). We anticipate that 3 patients will be accrued to Dose Level 1 without DLTs and that there will be no DLTs in Dose Level 2 cohort.

The primary study will be the phase II portion (Dose Level 2), where the primary endpoint is rate of resolution of pleural effusion. All patients treated at dose level 2 in Phase I or Phase II, will be included in analyses of safety and efficacy.

8.2 Sample Size and Accrual

The null hypothesis that the true rate of resolution of pleural effusion is 45% (Van Meyer 2011) will be tested against a two-sided alternative. The null hypothesis will be rejected if 15 or more responses are observed in 24 patients. A one group chi-squared test with a 0.100 two-sided significance level will have 80% power to detect the difference between the null hypothesis proportion of 45% and the alternative proportion of 70% when the sample size is 24. This sample size was calculated using nQuery Advisor v7.0.

For the phase II portion, sequential boundaries will be used to suspend the trial if excessive numbers of patients experience an unacceptable toxicity. If the study reaches a stopping boundary, it may be terminated by the PI, or submitted to the Data and Safety Monitoring Committee with a description of the failures to date and a rationale for why the study should be continued. An unacceptable toxicity is defined as any grade 3-5 adverse event attributed to therapy (with exceptions; see section 4.1.1 Definitions of Dose Limiting Toxicities (DLT) – Safety Run-in). The accrual will be halted if the number of patients with unacceptable toxicity is equal to or exceeds bn out of n patients with full toxicity follow-up (see table below). This is a Pocock type stopping boundary that assumes that an unacceptable toxicity rate of 0.20 is acceptable. If the true rate is equal to 0.20, the probability of crossing the boundary is 0.05.

Number of Patients, *n*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	-	-	3	4	4	4	5	5	6	6	6	7	7	7	8	8	8	8	9	9
Number of Patients, *n*	21	22	23	24	25	26	27	28	29	30										
Boundary, b_n	9	10	10	10	11	11	11	11	12	12										

Additionally, during the safety run-in (as indicated in section 4.1.1 of the protocol) if ≥2 subjects experience a DLT at either dose level then the study will be discontinued.

Any death (other than death related to progressive disease) within 30 days of study drug administration will result in the study pausing whereupon the study will be placed on hold until an appropriate evaluation of the cause of death and a plan of correction, if necessary, is established.

8.3 Data Analysis Plans

For the Phase I primary objective, we will summarize the toxicities of the patients. For the Phase II primary objective of estimating the rate of resolution of the malignant pleural effusion re-accumulation following IV nivolumab combined with intrapleural injection of talimogene laherparepvec, the percent of patients will be reported with a 95% confidence interval, and compared to the nullusing a chi-squared test.

Response rates and adverse events will be reported. Progression free survival, overall survival, and time to symptomatic pleural re-accumulation will be estimated using the Kaplan-Meier method. Available quality of life data will be summarized over the course of the study.

9.0 STUDY MANAGEMENT

9.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

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 an 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 who conducted the informed consent discussion.

9.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- 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 sub-investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation
- Financial Disclosures
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

9.3 Registration Procedures

All patients must be registered with the CPO at the University of North Carolina before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the UNC Study Coordinator. To register a patient, call the CPO at 919-966-4432 Monday-Friday 9:00 am – 5:00 pm EST or email the UNC Project Manager.

9.4 Data Management and Monitoring/Auditing

The CPO of the UNC LCCC will serve as the coordinating center for this trial. Data will be collected through a web based clinical research platform, OnCore®. All data will be collected and entered into OnCore® by research coordinators from UNC LCCC.

As an investigator initiated study, this trial will also be audited by the LCCC compliance committee every six or twelve months.

9.5 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.

9.5.1 Emergency Modifications

UNC investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC or their respective institution's IRB/IEC approval/favorable opinion.

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

9.5.2 Single Patient/Subject Exceptions

Eligibility single subject exceptions are not permitted for Lineberger Comprehensive Cancer Center Investigator Initiated Trials under any circumstances. Other types of single subject exceptions may be allowed if proper regulatory review has been completed in accordance with Lineberger Comprehensive Cancer Center's Single Subject Exceptions Policy.

9.5.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized 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).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- 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 or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs, please follow the guidelines below:

Protocol Deviations: UNC personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

Unanticipated Problems: Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the study personnel using the IRB's web-based reporting system.

9.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. 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. All protocol amendments will be submitted to Amgen for review.

The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

9.7 Record Retention

Study documentation includes all eCRFs, 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 all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. 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.

9.8 Obligations of Investigators

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 will be responsible for assuring that all the required data will be collected and entered into the eCRFs. 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 eCRFs will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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11.0 APPENDICES

11.1 Appendix A: ECOG Performance Status

Score	Definition
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 hours 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	In bed or chair more than 50% of waking hours
4	Totally confined to bed or chair – cannot carry on any self-care.
5	Dead

11.2 Appendix B: Cockcroft-Gault Formula

Males:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}.$$

Females:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

11.3 Appendix C: Treatment Algorithms for Nivolumab Therapy

Algorithms are presented for management of GI, renal, hepatic, pulmonary, endocrine, skin and neurological toxicities are provided.

GI Adverse Event Management Algorithm

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

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

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

Renal Adverse Event Management Algorithm

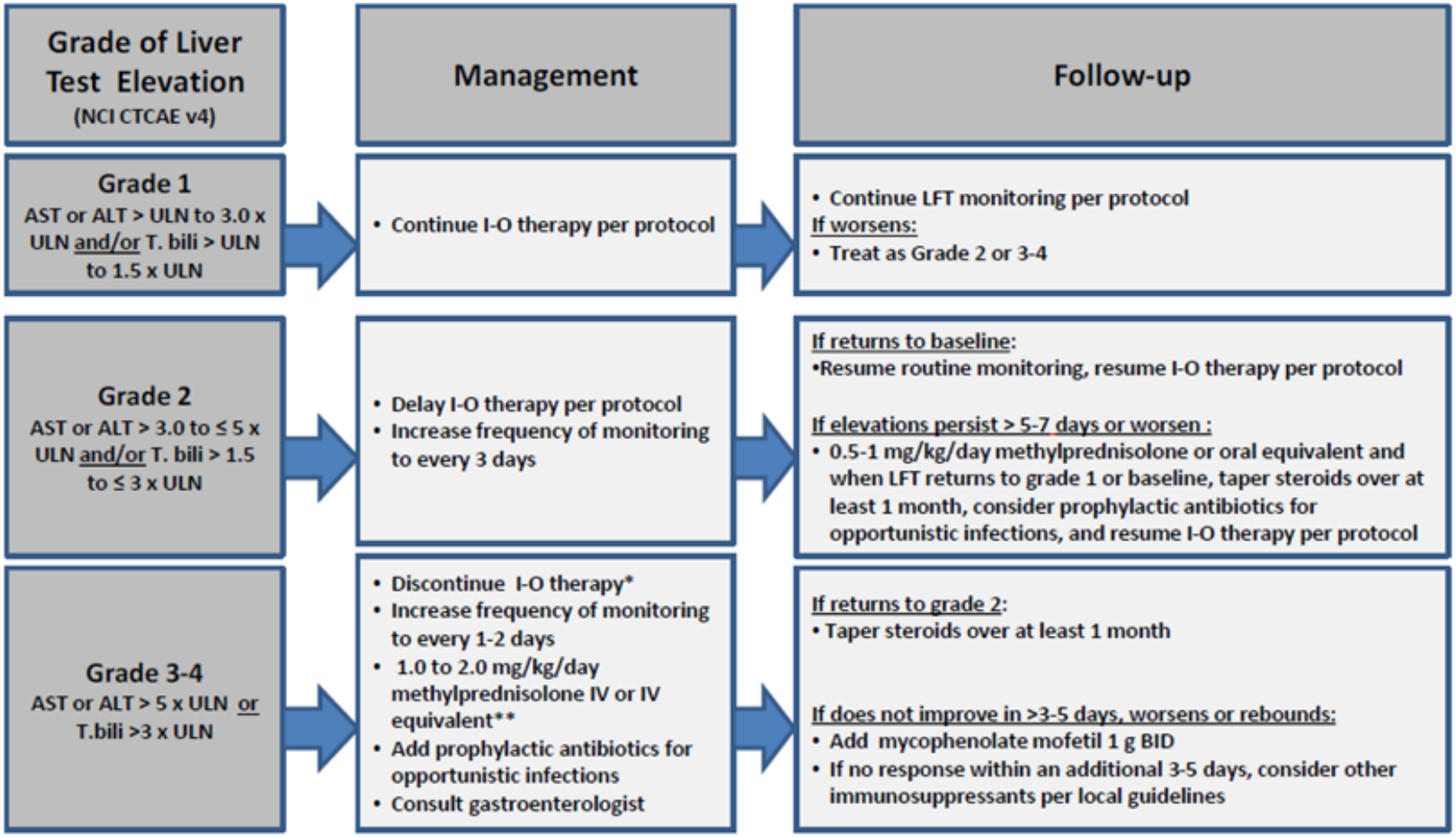
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	<u>If returns to baseline</u>: •Resume routine creatinine monitoring per protocol <u>If worsens:</u> •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	<u>If returns to Grade 1:</u> •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol <u>If elevations persist > 7 days or worsen:</u> •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	<u>If returns to Grade 1</u> : Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

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

Hepatic Adverse Event Management Algorithm

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



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

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

****The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.**

Pulmonary Adverse Event Management Algorithm

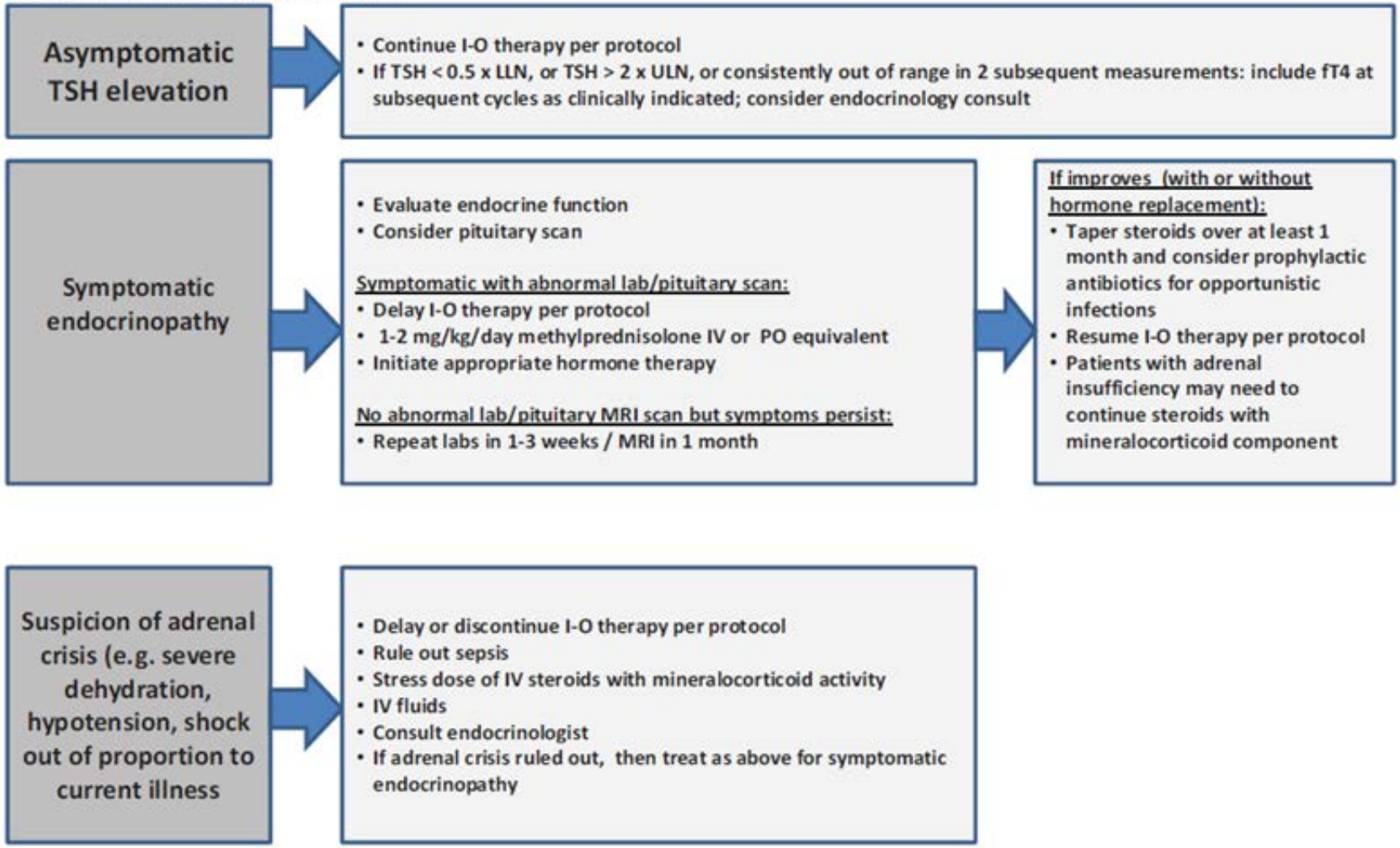
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression

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

Endocrinopathy Management Algorithm

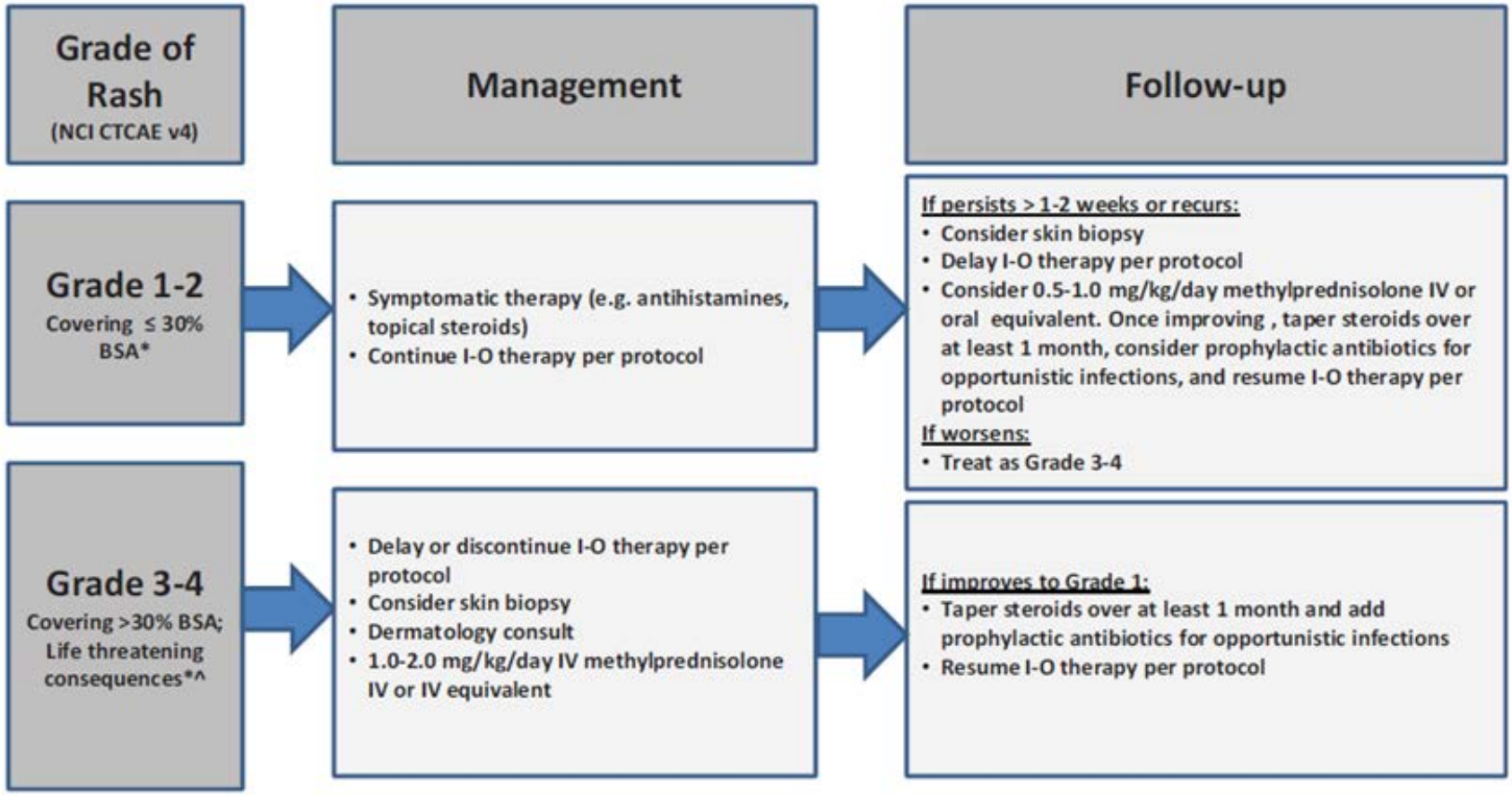
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

Skin Adverse Event Management Algorithm

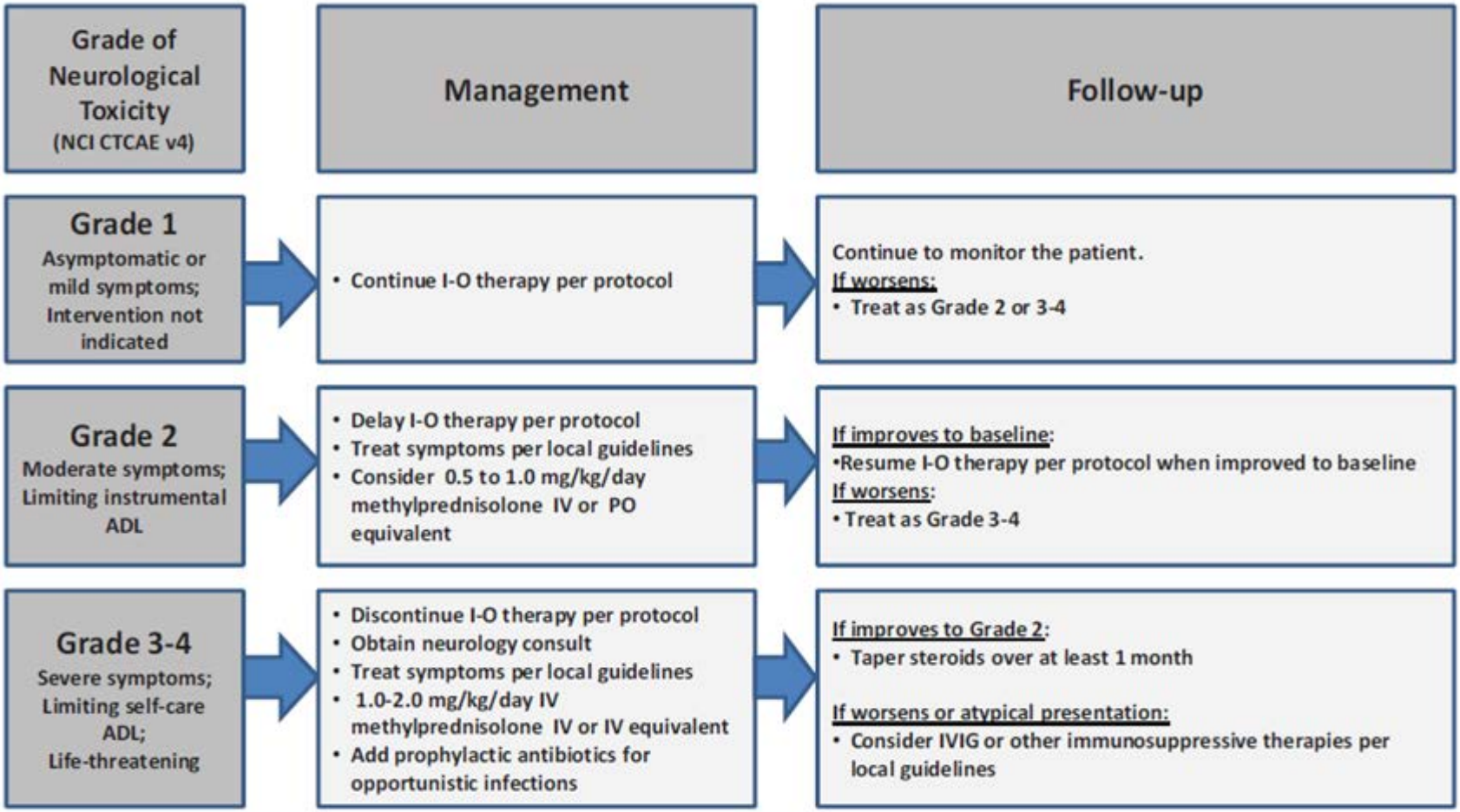
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm

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



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

11.4 Appendix D: Information Sheet for Trial Participants Study LCCC 1626

Information Sheet for Caregivers, Family Members or other Close Contacts to Clinical Trial Participants being given Talimogene Laherparepvec

Dear Family Member, Caregiver or Other Close Contacts:

A family member or close contact of yours has been enrolled in a clinical trial in which the Sponsor of the trial is collecting information regarding potential transfer of the investigational drug to close contacts. The clinical trial participants (your family member or close contact that is enrolled in the study) are being asked to provide information to you so that you understand what information the sponsor would like to collect from third parties. A close contact is considered a person that lives with the clinical trial participant (household member), care-giver, sex partner, or shares a bed with the clinical trial participant or conducts other activities that could involve exchange of bodily fluids through close physical contact

The purpose of this surveillance program is to identify any cases of suspected transmission to third parties by contact with talimogene laherparepvec treated subjects.

What is the Study Drug, Talimogene Laherparepvec?
Talimogene laherparepvec is an investigational drug that is being studied for the treatment of certain types of cancer. Talimogene laherparepvec contains a weakened form of the Herpes Simplex Virus Type 1 (the "cold sore" virus or "HSV-1").

Can talimogene laherparepvec be spread to family members or other close contacts and how long after the subject is treated is this possible?
Talimogene laherparepvec could potentially be spread to family or people who have close physical or intimate contact with the clinical trial participant after tumor(s) are injected with the study drug. So far there have been no reported cases in clinical trial participants who have received talimogene laherparepvec of spreading talimogene laherparepvec to family members or other close contacts. In clinical trials so far, no talimogene laherparepvec has been detected outside of the dressing that is placed on top of the site where it was injected.

The naturally occurring herpes simplex virus is not transmitted through the air or water droplets (such as when coughing or sneezing). Spreading occurs through direct contact from one person to another, particularly if a cold sore or genital sore is present. The virus is "shed" from active sores, and may be present even if the person has no symptoms (for example, kissing or having sexual intercourse or other intimate contact). It may also be spread by sharing a razor, towel, dish that has come in contact with a sore or bodily fluids.

Spreading (transmission) of talimogene laherparepvec may be similar to spreading of the naturally occurring herpes simplex virus. Unlike the naturally occurring virus, however, talimogene laherparepvec is administered into tumor lesions and is not expected to be able to replicate effectively in other noncancerous tissues. There have been no cases of spreading of talimogene laherparepvec to close contacts reported in clinical studies to date.

Small amounts of talimogene laherparepvec have been detected in subjects' blood and urine for up to 1 week after injection. In subjects treated with talimogene laherparepvec in clinical trials, talimogene laherparepvec has been found on the surface of the injected tumors, into the second week after the injection, but not on the outside of the dressings that covered these injection sites. Close contacts should avoid direct contact with the injection sites.

Close contacts or family members who are pregnant or have weakened immune systems should not touch injection sites, change dressings or clean injection sites. Newborns (babies who are one month or less in age) should not come into contact with the injection sites. Used dressings and cleaning materials should be kept away from pregnant women, newborns and those with weakened immune systems.

It is not known if talimogene laherparepvec virus can appear in mucous membranes of the lips and mouth or genitals of treated subjects. A clinical study is ongoing to determine if talimogene laherparepvec can be detected in the mouth area and genital area of treated subjects. To protect against possible sexual transmission of talimogene laherparepvec, subjects treated with talimogene laherparepvec or their partners should use latex condoms during sexual contact while on treatment and until 30 days after the end of treatment with talimogene laherparepvec. For those with latex allergies, polyurethane condoms may be used.

Spreading talimogene laherparepvec may be more likely if you have a break in your skin or a mucous membrane comes into contact with an injection site or body fluids of a treated subject. The clinical trial participant is given instructions on how to care for the lesions and areas that have been injected and how to avoid spreading talimogene laherparepvec to close contacts.

What Can Happen if I am Exposed to Talimogene Laherparepvec?

The naturally occurring type of HSV can cause a variety of symptoms, for example cold sores. Due to the changes in talimogene laherparepvec that make it different from the naturally occurring HSV, the chance of developing a herpes type infection is low, but you should know how to recognize these symptoms.

If talimogene laherparepvec were transmitted from a talimogene laherparepvec treated clinical trial participant to a third party, if any symptoms were observed, these might be expected to be similar to those that are typical with the naturally occurring herpes simplex virus such as:

- Sores around the mouth ("cold sore", "fever blister") or genitals ("genital sore").
- Blisters may develop on the fingers, ears or face.
- Eye infection (herpetic keratitis) with eye pain, light sensitivity, discharge from the eyes or blurry vision.
- Abdominal pain and infections, and inflammation inside the abdomen (infrequently).
- Rarely, serious infections of the brain (encephalitis) or spinal cord causing paralysis (unable to move) have been reported. Signs may include fever, confusion or other behaviour changes, headache, numbness and pain in the legs, constipation or difficulty with urination.
- Life-threatening infections (disseminated herpes) can develop in people with a weakened immune system.

After infection, the naturally occurring herpes virus may travel to spinal nerve roots. The virus can reactivate from the nerve roots and cause recurrent cold sores or other signs of infection as described above. Stress, other illness, or menstruation are common triggers for reactivation of the naturally occurring herpes simplex virus.

Who Should Not Have Contact with Talimogene Laherparepvec?

Persons with weakened immune systems, newborns and pregnant women should not come in contact with the lesions or areas that have been injected with talimogene laherparepvec or body fluids of treated subjects.

Close contacts or family members who are pregnant or have weakened immune systems should not touch injection sites, change dressings or clean injection sites. Newborns should not come into contact with the injection sites. Used dressings and cleaning materials should be kept away from pregnant women, newborns and those with weakened immune systems.

What Happens if There is Contact and Transmission Occurs?

Talimogene laherparepvec is sensitive to the antiviral drug acyclovir and any possible infection may be treated with this drug in its usual doses by your doctor.

If transmission of talimogene laherparepvec to a close contact is suspected, your doctor may want to determine if talimogene laherparepvec is present. This will depend on the symptoms observed, but if for example a cold sore appears, a swab may be taken for analysis. These tests will be most reliable if the testing is done within the first 3 days of symptoms occurring, but you should report to your health care provider at any time symptoms appear. Before any samples or information about your health or symptoms is collected your authorization will be requested in writing.

What Precautions Can Be Taken to Avoid Being Exposed to Talimogene Laherparepvec?

- Avoid direct contact with the treated subject's pleurX site and any fluid draining from the pleura.
- Wear gloves if changing dressings which cover the treated subject's pleurX catheter. Wear gloves when draining pleurX cathether starting from the first day of the study and as long as the cathether is in place, even if the subject is no longer receiving talimogene laherparepvec .
- Place all used dressings and cleaning materials for the pleurX in a sealed, plastic bag, and throw them away as household waste or return to the study site for disposal depending on local guidance.
- Before standard disposal, bleach should be added to fluid drained from the pleurX catheter after study initiation. Alternatively, it is acceptable to return the fluid to the investigators for safe disposal.
- The treated subject should avoid touching or scratching the pleurX site.
- The treated subject should always observe proper hygiene (wash hands with warm water and soap after touching the pleurX or any fluid that drains from the catheter to avoid spreading talimogene laherparepvec to other persons.
- If the treated subject develops any mouth or genital herpetic lesions (for example a painful fluid filled blister) during treatment with talimogene laherparepvec or during the follow-up period of the clinical trial, they should avoid activities that could increase the possibility of transmission such as sharing straws, drinking glasses or engaging in sexual activity until the lesions fully resolve.
    - The naturally occurring herpes simplex virus (HSV-1) can be transmitted through sexual contact. It is not known if talimogene laherparepvec will behave the same way, thus treated subjects or their partners should use a latex condom when engaging in sexual activity to prevent possible transmission of talimogene laherparepvec during the treatment with talimogene laherparepvec and until 30 days after the end of treatment. For those with latex allergies, polyurethane condoms may be used.
- Close contacts or family members who are pregnant or have weakened immune systems should not touch the pleurX site, pleural fluid or related bandages. Newborns should not come into contact with the pleurX site. Used dressings and cleaning materials should be kept away from pregnant women, newborns and those with weakened immune systems.

If you are accidentally exposed to talimogene laherparepvec, you should clean the affected area on your body with soap and water and/or a disinfectant. If you develop signs or symptoms of a herpes infection, call your doctor.

You or your doctor should report suspected herpetic lesions to Amgen (the manufacturer of talimogene laherparepvec) at **1-855-IMLYGIC** for the option of follow-up testing. Please indicate that you are a close contact of a patient participating in study **LCCC1626** at UNC.

If You/Minor Child Experience an Illness That Might be Related to Talimogene Laherparepvec

1. Please **IMMEDIATELY** let your doctor know.
2. Your close contact or family member should call their doctor and provide this information sheet. They should also call Amgen to report their signs or symptoms at **1-855-IMLYGIC. Please indicate that you/minor child are a close contact of a patient participating in study LCCC1626 at UNC.**
3. Please give this information sheet to the Doctor that is treating you and have them contact Amgen Medical Information **at 1-800-722-6436. Your doctor should indicate that you/minor child are a close contact of a patient participating in study LCCC1626 at UNC.**

11.5 Appendix E: Patient Catheter Drainage Diary

PleuRx® Drainage Schedule &
Patient Instructions

Please drain fluid through the catheter every other day using a one liter bottle. You should drain fluid until there is no more fluid coming out or you develop chest pain or persistent cough. You should drain no more than 1 liter (1000 cc) of fluid every other day.

Instructions to All Patients:

Keep track of each of your PleuRx® catheter drainages using the attached PleuRx® Catheter Diary. Complete all of the information in this diary unless the information does not apply to you, in which case you should enter N/A for Not Applicable. For the pain question, please enter a number from 0 to 10 describing any pain you had from your catheter drainage, where 0 equals No Pain and 10 equals the Worst Possible Pain. If you took any medicines for pain you had from your catheter drainage, please tell us what medicines you took and how much of those medicines you took in the Pain Med Details section. Finally, please tell us if you had any problems or complications from your catheter drainage and describe them in the Problem Details section. If you have any questions about your catheter drainage or completion of this diary, please talk with your physician.

If you drain <50ml of fluid from your PleuRx® catheter for three consecutive drainages, please call your doctor to see if the catheter needs to be flushed or removed.

Contact numbers:

Dr. Jared Weiss: 919-966-3856 (office)

Dr. Jason Akulian: 919-966-2531(office)

PleuRx® Catheter Diary

Date	Time	Drainag e Fluid	Drainage Fluid	Any Pain?	Pain (0-10)	Meds for Pain?	Pain Med	Any Problems/	Problem Details
				☐Yes ☐No		☐Yes ☐No		☐Yes ☐No	
				☐Yes ☐No		☐Yes ☐No		☐Yes ☐No	
				☐Yes ☐No		☐Yes ☐No		☐Yes ☐No	
				☐Yes ☐No		☐Yes ☐No		☐Yes ☐No	
				☐Yes ☐No		☐Yes ☐No		☐Yes ☐No	
				☐Yes ☐No		☐Yes ☐No		☐Yes ☐No	
				☐Yes ☐No		☐Yes ☐No		☐Yes ☐No	
				☐Yes ☐No		☐Yes ☐No		☐Yes ☐No	
				☐Yes ☐No		☐Yes ☐No		☐Yes ☐No	
				☐Yes ☐No		☐Yes ☐No		☐Yes ☐No	
				☐Yes ☐No		☐Yes ☐No		☐Yes ☐No	
				☐Yes ☐No		☐Yes ☐No		☐Yes ☐No	
				☐Yes ☐No		☐Yes ☐No		☐Yes ☐No	

Page __ of ___

11.6 Appendix F: Borg Scale

*Instruction for Borg Dypsnea Scale

Use this scale to rate the difficulty of your breathing.

It starts at number 0 where your breathing is causing no difficulty at all and progresses through to number 10 where your breathing difficulty is maximal.

How much difficulty is your breathing causing you right now?

0	**Nothing at all**
0.5	**Very, very slight (just noticeable)**
1	**Very slight**
2	**Slight**
3	**Moderate**
4	**Somewhat severe**
5	**Severe**
6	
7	**Very severe**
8	
9	**Very, very severe (almost maximal)**
10	**Maximal**

11.7 Appendix G: NYHA – Functional Classification System

Class	Symptoms
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
Class II	Slight limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.