A Phase I Trial of Talimogene Laherparepvec for the Treatment of Peritoneal Surface Malignancies (TEMPO)

Trial: NCT03663712

Protocol

November 8, 2022

A Phase I Trial of Talimogene Laherparepvec for the Treatment of Peritoneal Surface Malignancies (TEMPO)

Lead Principal Investigator:

Dan Blazer III, MD
Duke University Medical Center
DUMC 3505
Durham, NC 27710

Study Chair:

John H. Stewart, IV, MD, MBA
Louisiana State University, New Orleans

Co-Principal Investigators:

Niharika B. Mettu, MD, PhD
Duke University Medical Center
DUMC 3505
Durham, NC 27710

Edward A. Levine
Wake Forest University School of Medicine
1 Medical Center Boulevard
Winston-Salem, NC 27013

Shannon MacLaughlan, MD
University of Illinois College of Medicine at Chicago
818 South Wolcott Avenue
Chicago, IL 60612

Supported by:

Amgen

PROTOCOL VERSIONS

Version Number	Version Date
Version 1.0/ Initial	*05 Sept 2018*
Version 2.0/ Amendment 1	*01 Mar 2019*
Version 3.0/ Amendment 2	*24 May 2019*
Version 4.0/ Amendment 3	*01 Oct 2019*
Version 5.0/ Amendment 4	*05 May 2020*
Version 6.0/ Amendment 5	*06 Jul 2020*
Version 7.0/ Amendment 6	*21 Sep 2020*
Version 8.0/ Amendment 7	*23 Dec 2020*
Version 9.0/ Amendment 8	*20 Sep 2021*
Version 10.0/ Amendment 9	*22 Dec 2021*
Version 11.0/ Amdendment 10	*08 Nov 2022*

SPONSOR CONTACT INFORMATION

Lead Principal Investigator (PI):

Dan Blazer III, MD
Phone: 919-668-1861
Email: trey.blazer@duke.edu

Study Chair:

John H. Stewart, IV, MD, MBA
Louisiana State University, New Orleans
1542 Tulane Avenue, Room 747A
New Orleans, LA 70112
Phone: 336-306-0181
Email: jste17@lsuhsc.edu

Co-Principal Investigator (PI):

Niharika B. Mettu, MD, PhD
Duke University Medical Center
DUMC 3505
Durham, NC 27710
Phone: 919-668-1861
Fax: 919-668-3037
Pager: 919-684-8111
Email: niharika.mettu@duke.edu

Edward A. Levine
Wake Forest University School of Medicine
1 Medical Center Boulevard
Winston-Salem, NC 27012
Phone: 336-716-0545
Email: elevine@wakehealth.edu

Shannon MacLaughlan, MD
University of Illinois College of Medicine at Chicago
818 South Wolcott Avenue
Chicago, IL 60612
Email : smacdav.uic.edu

PROTOCOL SYNPOSIS

Title

A Phase I Trial of Talimogene Laherparepvec for the Treatment of Peritoneal Surface Malignancies (TEMPO)

Objectives

Primary Objective

1. To evaluate the toxicity profile of intraperitoneal talimogene laherparepvec in patients with peritoneal surface dissemination from gastrointestinal, fallopian tube, ovarian, or primary peritoneal tumors.

Secondary Objectives

1. To evaluate the pharmacokinetic profile and viral shedding of talimogene laherparepvec by measuring viral load in plasma and urine as well as viral load in peritoneal washings.

Exploratory Objectives

1. To evaluate the magnitude and duration of tumor response.
2. To evaluate the time to tumor progression as measured by radiographic imaging, clinical symptoms, and/or tumor marker levels.
3. To describe the clinical activity of talimogene laherparepvec, as measured by overall survival.
4. To evaluate the changes in peritoneal cavity leukocyte populations after the treatment of peritoneal surface dissemination of gastrointestinal, fallopian tube, ovarian or primary peritoneal cancers with talimogene laherparepvec.

Patient Population

Patients must have measurable stage IV peritoneal surface dissemination of gastrointestinal or ovarian cancer on radiographic imaging that cannot be completely resected at time of abdominal exploration or elevated CEA/CA-125 as markers of disease.

Study Design

This is a non-randomized, open-label Phase I trial in patients with Stage IV peritoneal surface dissemination from gastrointestinal, fallopian tube, ovarian, or primary peritoneal tumors enrolled at the University of Illinois College of Medicine at Chicago, Duke Cancer Institute, and select external collaborating institutions. All subjects will complete an extensive medical history, baseline physical examination and clinical assessment to ensure subject eligibility requirements (see Eligibility Criteria for details) within 4 weeks of starting study drug. All eligible patients must have a peritoneal catheter placed prior to the initiation of therapy.

There will be two stages, a Dose Escalation Cohort, and a Dose Expansion Cohort. All patients will receive an initial seroconversion dose of talimogene laherparepvec on Cycle 1 Day 1 to enable seroconversion as described in the currently approved treatment protocol for the treatment of cutaneous melanoma. Three weeks after the seroconversion dose, patients will receive talimogene laherparepvec at the dose level for the cohort in which they are enrolled. They will be treated every 2 weeks for up to 4 doses (in addition to the initial seroconversion

dose, which all patients will receive). The length of the first cycle is 5 weeks and subsequent cycles are 2 weeks in duration.

In the Dose Escalation Cohort, there will be up to three dose levels explored in a standard '3+3' dose escalation design. Three subjects will be accrued at the starting dose level. If no DLTs are seen at that level, three subjects will be enrolled at the next dose level. If one of three subjects has a DLT at any dose level, an additional three subjects will be enrolled at that dose level. If one of six subjects experience DLT, then escalation may continue. If two or more subjects have DLT at any dose level, then that dose level will be considered to have unacceptable toxicity, the next lower dose level will have additional subjects enrolled. Up to six subjects will be enrolled at the maximum tolerated dose (MTD) before proceeding to the expanded cohort.

The Dose Expansion cohort will enroll subjects at the MTD and follow the treatment scheme described above.

Number of Subjects

The Dose Escalation Cohort will enroll 6 to 18 subjects.

The Dose Expansion Cohort will enroll 6 subjects.

A total of 12 to 24 evaluable subjects will be accrued to assess the safety and tolerability of intraperitoneal talimogene laherparepvec.

Estimated Length of Study Participation

Estimated duration of subject enrollment is 5 months.

Subjects may continue to receive study treatment until they receive up to 4 doses after the initial seroconversion dose, experience unacceptable drug-related toxicity, or disease progression. For subjects that discontinue study treatment with no documented disease progression and no subsequent anti-cancer treatment, they will be followed every 12 weeks or as clinically indicated with tumor evaluations until disease progression or start of new anti-cancer therapy is documented. All subjects will be followed for survival for 1 year after completing treatment.

Study Drug Regimen

All patients will receive an initial seroconversion dose of intraperitoneal talimogene laherparepvec $4x10^6$ PFU on Cycle 1 Day 1 to enable seroconversion as described in the currently approved treatment protocol for the treatment of cutaneous melanoma. Three weeks after the initial seroconversion dose, patients will receive talimogene laherparepvec at the dose level for the cohort for which they are enrolled every 2 weeks for up to 4 doses (in addition to the initial seroconversion dose, which all patients will receive). The length of the first cycle is 5 weeks and subsequent cycles are 2 weeks in duration.

In the Dose Escalation Cohort, three subjects will be enrolled at the starting dose of $4x10^6$ PFU, and the dosing will continue in the standard '3+3' dose escalation scheme. If the starting dose is tolerated, enrollment will continue at $4x10^7$ and $4x10^8$ PFU. Once the MTD is determined, six subjects will be enrolled to the Dose Expansion Cohort at the MTD. All subjects will be dosed with talimogene laherparepvec IP once every 2 weeks for up to 4 doses (in addition to the initial seroconversion dose, which all patients will receive).

Study Assessments

Safety: Toxicity and safety assessments will be performed weekly during the 5 weeks, then every 2 weeks for up to 4 treatment visits. These assessments will include vital signs, ECOG performance status, medical history, physical examination, complete blood count (CBC), biochemistry, creatinine, AST, ALT, and bilirubin. Toxicities will be recorded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. General symptom management and supportive care will be provided as clinically indicated to ensure optimal patient care. After discontinuation of study treatment, subjects will have toxicity and safety assessments 30 days after last dose of study drug.

Tumor Assessments

Restaging scans and blood tumor markers will be repeated at the end of cycle 4, after receipt of the fifth dose of study drug. Tumor response will be assessed using treating physician's discretion, based on a composite of RECIST 1.1 measurements, blood tumor markers (CEA or CA-125), measurements of abdominal girth, and/or clinical response.

For subjects who discontinue study treatment with no documented disease progression and no subsequent anti-cancer treatment, they will be followed every 12 weeks or as clinically indicated with tumor evaluations consisting of restaging scan with RECIST 1.1 evaluation and blood tumor markers, until disease progression or start of new anti-cancer therapy is documented

Correlative Studies

The association between biomarker expression and clinical outcomes will be explored with the following blood and tumor tissue specimen collections and specified time points from all subjects:

- *Tumor Tissue*. If available, archived FFPE tumor samples will be obtained from all subjects at the end of the study, upon PI request.
- *Viral Load*. Blood and urinewill be collected at baseline (prior to seroconversion dose on Cycle 1 Day 1), Cycle 1, Day 8, Cycle 1 Day 15, prior to treatment on Cycle 1 Day 22, Cycle 1 Day 29, prior to treatment Cycle 2 Day1, prior to treatment on Cycle 3 Day 1, prior to treatment on Cycle 4 Day 1, at disease progression or off treatment, and 30-day off treatment follow-up. Peritoneal fluid will be collected at at baseline (prior to seroconversion dose on Cycle 1 Day 1), prior to treatment Cycle 2 Day 1, prior to treatment on Cycle 4 Day 1, at disease progression or off treatment, and 30-day off treatment follow-up
- *Peritoneal Cytokine Levels*. Collected at baseline (prior to seroconversion dose on Cycle 1 Day 1), prior to treatment on Cycle 2 Day 1, prior to treatment on Cycle 4 Day 1, and at disease progression or off treatment, and 30-day off treatment follow-up.
- *Immune Cells.* Immune cells from blood and peritoneal washings will be collected at baseline (prior to seroconversion dose on Cycle 1 Day 1), prior to treatment on Cycle 2 Day 1, prior to treatment on Cycle 4 Day 1, and at disease progression or off treatment, and 30-day off treatment follow-up.
- *Plasma*. Collected at baseline (prior to seroconversion dose on Cycle 1 Day 1), prior to treatment on Cycle 1 Day 22, prior to treatment on Cycle 2 Day 1, prior to treatment on Cycle

3 Day 1, prior to treatment on Cycle 4 Day 1, and at disease progression or off treatment, and 30-day off treatment follow-up.

- *Pharmacogenomics*. Subjects will have whole blood collected at baseline.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Events
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
CBC	Complete Blood Count
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
DC	Dendritic Cells
DLT	Dose Limiting Toxicity
DRR	Durable Response Rate
GM-CSF	granulocyte macrophage colony-stimulating factor
HgB	Hemoglobin
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HSRC	Human Subject Research Compliance
HSV-1	Herpes Simplex Virus Type-1
HNSCC	Head and Neck Squamous Cell Carcinoma
IRB	Institutional Review Board
irRC	immune-related Response Criteria
LFTs	Liver Function Tests
LD_{50}	Median Lethal Dose
MTD	Maximum Tolerated Dose
NOAEL	No Adverse Effect Level
OS	Overall Survival
PC	Peritoneal carcinomatosis
PCR	Polymerase Chain Reaction
PFS	Progression-Free Survival
PR	Partial Response
RPTD	Recommended Phase Two Dose
SAE	Severe Adverse Events
SC	Subcutaneous
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SCID	Severe Combined Immunodeficiency
SD	Stable Disease
SOC	Safety Oversight Committee
$TCID_{50}$	50% Tissue Culture Infective Dose
TVEC	Talimogene Laherparepvec Virus
ULN	Upper Limit of Normal

1.0 INTRODUCTION

1.1 Background

Peritoneal carcinomatosis (PC) represents a widespread metastatic dissemination throughout the abdomen and pelvis of many organ-based malignancies. Cancers of the ovary, colon, stomach, and appendix are common primary tumor sites that give rise to PC[1]. There are approximately 22,000 new cases of epithelial ovarian cancer in the United States in 2014. Because 70% of patients with ovarian cancer present with advanced stage disease[1], epithelial ovarian cancer is the leading cause of gynecologic cancer death at 14,000 deaths each year. Fallopian tube carcinoma is a rare gynecological cancer with approximately 300-400 new cases annually. It is often included as a subset of epithelial ovarian cancer, along with primary peritoneal cancer, as the clinical course and treatment of these three cancers are the same [21]. Recent literature suggests that some high-grade serous ovarian cancer (HGSOC) originates in the fallopian tube [21,22]. Similarly, colon cancer presents with metastases to the peritoneum in up to 15% of patients at the time of diagnosis[2], and in patients treated curatively, PC is involved at recurrence in up to 50% of patients[1]. PC from gastric cancer is discovered at the time of initial surgery in 10-20% of patients and in up to 60% of patients who have undergone a curative resection for T3/T4 tumors[3]. Although the incidence of appendiceal cancer is only between 0.1-1 in 1,000,000 people annually, patients are usually asymptomatic until aggressive PC has been established[4]. Unfortunately, PC is uniformly a terminal disease with a median survival of six months[3]. Systemic chemotherapy is palliative and generally provides limited improvement in survival[1]. Intraperitoneal therapy provides a pharmacokinetic advantage in the treatment of local regional disease relative to systemic therapy due to the peritoneal-plasma partition[5].

Current experience suggests that only the minority of patients derive any clinical benefit from the current approach of cytoreduction and heated intraperitoneal chemotherapy because few are able to undergo complete cytoreduction. Therefore, the majority of patients have limited therapeutic options and frequently succumb to bowel obstruction, subsequent malnutrition and death. Oncolytic viral agents such as oncolytic talimogene laherparepvec virus (TVEC) that effectively initiate tumor cell killing and induce robust and durable anti-tumor immune responses is key to developing successful oncolytic viral therapies for cancer[6]. Talimogene laherparepvec is attenuated for virulence and has both oncolytic and immune-stimulating properties[7]. The virus selectively replicates within tumors, rupturing them and producing granulocyte macrophage colony-stimulating factor (GM-CSF), which enhances systemic, specific antitumor immune responses[8]. Current data suggests that talimogene laherparepvec activates multiple subsets of dendritic cells (DC) to produce Type I IFN, pro-inflammatory cytokines and T cell co-stimulatory molecules that are key to driving innate and adaptive anti-tumor immune responses. Talimogene laherparepvec has been utilized in two clinical trials of patients with advanced melanoma. In a phase 2 study[7] of 50 advanced melanoma patients, talimogene laherparepvec response rates were 16% complete, 10% partial, 4% surgical complete and another 20% had stable disease for at least 3 months. Three more patients achieved complete responses on an extension protocol. Overall survival was 54 and 52% at 1 and 2 years, respectively. Systemic immunotherapeutic effects were evidenced by responses in both injected and uninjected lesions[7]. In the phase 3 OPTiM trial[9], Kaufman et al. compared talimogene laherparepvec versus subcutaneous GM-CSF in 436 stage IIIB/C and IV melanoma patients who had injectable and unresectable disease. Complete responses were reported in 0.7% of GM-CSF patients and in 10.8% of talimogene laherparepvec patients. The treatment difference of 14.1% (95% CI 8.2, 19.2) was highly significant ($P < 0.0001$). The durable response rate for talimogene laherparepvec was 16% (95% CI 12%, 21%) and 2% for GM-CSF (95% CI 0%, 5%, $P < 0.0001$). Median overall survival was 18.9 months (95% CI 16.0, 23.7) in the GM-CSF group and 23.3 months (95% CI 19.5%, 29.6) in the T-VEC group ($P = 0.051$)[10].

1.2 Study Drug

1.2.1 Talimogene Laherparepvec (TVEC)

Talimogene Laherparepvec (IMLYGIC^{TM}, formerly known as OncoVEX^{GM-CSF}) is an investigational, oncolytic immunotherapy based on a modified herpes simplex virus type-1 (HSV-1) that is designed to selectively replicate in tumor tissue and to stimulate a systemic antitumor immune response[20]. In talimogene laherparepvec, the HSV-1 viral genes ICP34.5 (the "neurovirulence factor" that promotes viral replication in normal cells with an intact anti-viral response but is not required for replication in tumor tissue in which anti-viral responses are often defective) and ICP47 (which blocks antigen presentation by major histocompatibility complex molecules of infected cells) have been deleted. In addition, deletion of ICP47 leads to increased and earlier expression of US11 which enhances viral replication in infected tumor cells. The coding sequence for human granulocyte macrophage colony stimulating factor (GM-CSF) is inserted in place of ICP34.5, to enhance the immune response to tumor antigens released during oncolysis. Intralesional administration of talimogene laherparepvec results in oncolysis of cells within injected tumors. Iterative viral replication within permissive tumor tissue results in lytic cell destruction and local release of progeny virus as well as of tumor cell antigens. GM-CSF, the product of the viral transgene, is also produced locally to recruit and stimulate antigen presenting cells which, in addition to relevant tumor-derived antigens, are required for the initiation of a systemic antitumor immune response. Overall, this strategy is expected to result in the destruction of injected tumors via oncolysis and also uninjected sites of disease (including micro-metastases) via a systemic antitumor immune response, to curtail tumor progression and to reduce local and distant tumor recurrence.

Talimogene laherparepvec is approved for use by direct injection in to tumors. In the clinical studies described thus far, dose schedules may vary depending upon the tumor type and whether talimogene is administered as monotherapy or as part of combination therapy. For melanoma, an optimized monotherapy dosing regimen consisting of a first dose of 10^6 plaque forming units (PFU)/mL (total injected volume dependent on injectable tumor burden is used. Optimum combination therapy regimens are still being evaluated.

Talimogene laherparepvec has been tested for efficacy in a variety of in vitro (cell line) and in vivo murine tumor models and has been shown to eradicate tumors or substantially inhibit their 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.

Talimogene laherparepvec is approved in multiple regions for the treatment of unresectable melanoma that is regionally or distantly metastatic.

As of 26 October 2016, 15 clinical studies (including 2 extension studies) have been or are being conducted in several advanced tumor types (advanced solid tumors, melanoma, head and neck squamous cell carcinoma [HNSCC], pancreatic cancer, and hepatocellular carcinoma). An estimated total of 893 subjects have received talimogene laherparepvec in clinical studies as of 26 October 2016.

1.2.1.1 Product Description

Talimogene laherparepvec is a modified HSV-1 containing the gene coding for human GM-CSF. Wild type HSV-1 is an alpha herpes virus that can infect a wide range of cell types. HSV-1 consists of a large double-stranded linear DNA genome of approximately 152 kb that is packaged into an icosahedral nucleocapsid approximately 125 nm in diameter[20]. HSV-1 is an enveloped virus with an amorphous

structure between the nucleocapsid and envelope known as the tegument that contains virus proteins important in the early stages of the infection process. The size of the complete virion varies but the average virion diameter is 186 nm, or approximately 225 nm if the glycoprotein spikes are included. Talimogene laherparepvec has been extensively characterized using growth curves, buoyant density gradients, restriction mapping, size exclusion chromatography, epitope mapping, western blotting, and electron microscopy. Additionally, the talimogene laherparepvec genome has been sequenced.

1.2.1.2 Preclinical and Clinical Trial Experience

For complete study information, refer to the current Talimogene Laherparepvec Investigator's Brochure (IB).

Nonclinical Pharmacology Summary[20]

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 laherparepvec and its murine analog, OncoVex$^{mouseGM\text{-}CSF}$.

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. 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 cyclosporine.

Talimogene laherparepvec has been tested to evaluate the combined effects of either radiation or chemotherapy in preclinical studies. Both combinations were tolerated could support potential clinical studies with these other agents for the treatment of cancer.

Nonclinical Toxicology

The toxicology program evaluated the safety of talimogene laherparepvec following repeated subcutaneous (SC) dosing for up to 13 weeks in the BALB/c mouse. Additional studies evaluated the safety of talimogene laherparepvec following a single intra-arterial dose (via the hepatic artery in the rat (Study 4648-00031), a single intraprostatic dose in the dog (Study 4648-00032), and repeated intravenous (IV) dosing in an embryo-fetal developmental toxicity study in the BALB/c mouse (Study 117250). These pivotal single- and repeat-dose toxicology and embryo-fetal development studies were performed in accordance with Good Laboratory Practice (GLP) regulations, and Office of Economic Cooperation and Development standards. Supplemental, non-GLP compliant studies evaluated neurovirulence with talimogene laherparepvec following direct intra-cerebral injection (Study 4648-00004) or intranasal instillation in the BALB/c mouse (Study 4648-00014) and the in virto sensitivity of talimogene laherparepvec to acyclovir as a standard anti-viral therapy (Study 4648-00024). Additionally, the safety of a surrogate HSV-1 construct expressing murine GM-GSF (OncoVEX$^{mGM\text{-}CSF}$) administered as a repeated SC injection was evaluated in BALB/c mice [Study 4648-00052 (non-GLP-compliant) and 4648-00029 (GLP-compliant)]. The tolerability of talimogene laherparepvec was evaluated following repeated intratumoral injection in HT-29 tumors implanted into CB17 severe combined immunodeficiency (SCID) mice (deficient in T and B lymphocytes and BALB/c nude mice (deficient in T lymphocytes and partially deficient in B cell function).

High and multiple doses of talimogene laherparepvec, up to 10^7 PFU/animal, were well tolerated in immune competent mice following SC, IV, or intralesional injection. A dose margin of 60-fold (based on body weight) for general safety is estimated using the no adverse effect level (NOAEL, also the highest dose tested in Studies 4648-00027, 4648-00028, 4648-00029) following repeated SC injection in mice compared with the maximum dose to be administered to patients. 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.

Key findings following repeated SC administration of talimogene laherparepvec included reversible inflammation at the injection site; increased total white blood cells, neutrophils and lymphocytes (all reversible); and 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 antibodies. No evidence of overt toxicity to any cell type or organ, and no evidence of virally-associated neuropathology/neurovirulence were observed in animals treated with talimogene laherparepvec.

Intravenous injection of talimogene laherparepvec at doses of 10^5, 10^6, or 10^7 PFU/dose on gestation days 6, 9, 12, and 15 had no impact on embryo-fetal viability and development, or skeletal variations or malformations as assessed on gestation day 18. Assessment of maternal blood demonstrated a dose-dependent increase in viral DNA concentration, and was detected in 1 of 4 pooled fetal samples in the high dose group on GD18 at <0.001% of maternal levels (study 117250).

HSV-1 strains in which the ICP34.5-encoding gene has been deleted demonstrate 10,000 to 1,000,000-fold less neurovirulence as compared to wild-type HSV-1(Chou et al, 1990; Bolovan et al, 1994). Across all studies, no evidence of virally-associated neuropathology/neurovirulence has been observed in any animal treated with talimogene laherparepvec. To evaluate whether the deletion of ICP34.5 in talimogene laherparepvec was associated with attenuated neurovirulence as reported for other ICP34.5-deleted HSV-1 strains, two studies were conducted to evaluate the toxicity of talimogene laherparepvec following direct intracerebral injection or nasal instillation in mice, respectively (Studies 4648-00004 and 4648-00014). Talimogene laherparepvec demonstrated approximately 10,000-fold less neurovirulence at the median lethal dose (LD_{50}) following intracerebral injection as compared to that reported for wild-type HSV-1 (MacLean et al, 1991). No mortality was seen in mice treated with talimogene laherparepvec via intranasal administration despite use of doses 100-fold greater than those doses associated with the LD_{50} for wild-type HSV-1 (Hudson et al, 1991); the absence of toxicity with talimogene laherparepvec at the doses tested in this study preclude comparisons of the relative neurovirulence of talimogene laherparepvec compared to wild-type HSV-1 in mice.

Severe combined immunodeficiency mice were treated with 3 doses of 5 x 10^6 PFU talimogene laherparepvec via intratumoral injection on days 1, 4, and 7. All SCID mice treated with talimogene laherparepvec were found dead or were euthanized between days 18 and 21 after the initial seroconversion dose, and 7 animals were submitted either for complete necropsies or select tissues were collected. Similarly, across a series of pharmacology studies evaluating the activity of talimogene laherparepvec towards pediatric tumors, a subset (approximately 14%) of nude mice died or required early euthanasia. Viral inclusion bodies and/or necrosis in enteric neurons in the gastrointestinal tract, adrenal gland, and skin were observed in both mouse strains; and in pancreatic Islet cells, eye, pineal gland, and brain of SCID mice. Systemic infection and lethality in nude mice treated with talimogene laherparepvec was observed at doses that are 10- to 100-fold higher than those that result in 100% lethality in nude mice treated with wild-type HSV-1 (Hayashida et al, 1982; Yamamoto et al, 1985), indicating that talimogene laherparepvec is attenuated for causing systemic infection. These data

indicate an important role of host defenses, including both T and B cell function, in the immune response to talimogene laherparepvec and HSV-1 viruses. The viral thymidine kinase gene, responsible for phosphorylating acyclovir to acyclovir-monophosphate, is maintained, rendering talimogene laherparepvec sensitive to anti-viral therapy (Study 4648-00024).

Clinical Trial Summary[20]

As of 26 October 2016, 15 clinical studies have been or were being conducted with an estimated total of 893 subjects. Seven studies were complete, 7 were ongoing, and 1 was terminated early. A non-interventional registry study was ongoing to investigate the long-term survival and safety of subjects previously treated with talimogene laherparepvec in any study.

Pharmacodynamics and Pharmacokinetics

Six clinical studies were conducted to characterize the dosing regimen, kinetics, viral shedding, clearance, anti-HSV-1 serostatus, and GM-CSF expression in tumor tissue of talimogene laherparepvec in subjects with metastatic melanoma and other cancer types, including the first-in-human study (Study 001/01). Five other studies primarily designed to evaluate efficacy and/or safety provided supportive data (Studies 002/03, 004/04, 005/04, 005/05 and 20120324).

The biodistribution pattern of talimogene laherparepvec in blood and urine demonstrated consistently across studies that low copy numbers of viral DNA were sporadically detected in blood samples from 33% of subjects and urine samples from 22% of subjects from 1 hour to 1 week after intralesional injection. Blood and urine samples were negative by 2 weeks post-injection in those subjects for whom additional samples were available. The copy numbers of virus detected in blood and urine in all subjects at all collection time points was far lower than those present in the doses administered during treatment.

Viral shedding was assessed by the collection of swab samples from the surface of injected tumors and the exterior dressing. The samples were analyzed by a plaque assay or 50% tissue culture infective dose ($TCID_{50}$; Study 20120324 only) to determine if any infectious virus was present and to assess whether the occlusive dressings provided adequate containment for virus present at the tumor surface. The infectivity assays did not distinguish between wild-type HSV-1 and talimogene laherparepvec. It was assumed that a positive assay result indicated the presence of talimogene laherparepvec since the probability that wild-type HSV-1 was present on the surface of injected tumors and/or dressings would be very low.

The most comprehensive set of samples (ie, in terms of the number of time points tested) was obtained from Study 001/01. Overall, at any time point, a low percentage of subjects (13% [4/30]) had swabs that were positive for virus at the tumor site. These samples were further tested by a specific custom polymerase chain reaction (PCR) assay to distinguish between talimogene laherparepvec and wild-type HSV; it was determined that the virus detected in 3 of the swab samples was talimogene laherparepvec and not wild-type HSV. Results from Studies 002/03 and 004/04 were consistent with those from Study 001/01.

All swabs of the exterior of the dressing were negative at all time points tested across all studies. Thus, it appeared that the dressings were used effectively and prevented shedding of any virus from the tumors into the environment.

Efficacy

Analyses of efficacy have been conducted for 5 studies (001/01, 002/03, 002/03-E, 005/05, and 005/05-E) with talimogene laherparepvec as monotherapy for various tumors and for 4 studies (004/04, 006/09, 20110264, and 20110265) with talimogene laherparepvec as combination therapy for various tumors.

- Talimogene laherparepvec demonstrated initial biological activity as monotherapy (doses as low as 106 PFU/mL) in subjects with advanced solid tumors with metastases in the skin or SC tissue as evidenced by necrosis or apoptosis in tumor biopsies (Study 001/01).
- Talimogene laherparepvec resulted in an improvement in durable response rate (DRR), a primary endpoint of Study 005/05 (defined as complete response [CR] or partial response [PR] maintained for ≥ 6 months continuously and which had its onset on the first 12 months of treatment) compared with GM-CSF. At the primary analysis of overall survival (OS), a secondary endpoint of Study 005/05, median OS was 23.3 (95% CI: 19.5, 29.6) months in the talimogene laherparepvec arm and 18.9 (95% CI: 16.0, 23.7) months in the GM-CSF arm (hazard ratio [HR] 0.79; 95% CI: 0.62, 1.00; p = 0.051). At final analysis, with an additional follow-up of 5 months (median 49 months [range, 37–63]), median OS remained 4.4 months longer for T-VEC compared with GM-CSF (23.3 months, 95% CI: 19.5 to 29.6 vs 18.9 months, 95% CI: 16.0, 23.7; HR 0.79, 95% CI: 0.62, 1.00, P = 0.0494, descriptive). Results from the phase 2 study in melanoma (002/03) also support the efficacy of talimogene laherparepvec for the treatment of melanoma.
- The high proportion of tumors that decreased in size and high rate of histopathological response at surgery suggested clinical activity with talimogene laherparepvec in combination with cisplatin and radiation in subjects with SCCHN (Study 004/04). Further investigations in a larger sample set were planned in the phase 3 study (006/09); however, this phase 3 study was terminated in July 2011 in light of emerging evidence regarding the influence of human papillomavirus status and smoking on prognosis following chemoradiation, and effects of these factors on the likelihood of study success.
- In the phase 1b portion of 20110264, a phase 1b/2 study evaluating the combination of talimogene laherparepvec and ipilimumab (Puzanov et al, 2016), 18 of 19 patients (more than half with visceral metastases) received both talimogene laherparepvec and ipilimumab in combination. With a median tumor follow-up time of 15.6 months, median PFS was not yet reached with 50% of patients still without progression at 18 months, and median OS was not yet reached with 67% of patients still alive at 18 months. Objective response rate per immune-related response criteria (irRC) was 50%; CR rate was 22%; disease control rate was 72%; and DRR was 44%.
- In the phase 1b portion of Study 20110265, a phase 1b/3 study evaluating the combination of talimogene laherparepvec and pembrolizumab (Long et al, 2016), 21 subjects received talimogene laherparepvec and pembrolizumab in combination. At the time of the primary analysis, the confirmed objective response rate and complete response rate were 57.1% and 23.8%, respectively, per irRC. The unconfirmed objective response rate and complete response rate were 66.7% and 28.6%, respectively. Median PFS was not reached, with 71% of subjects progression free at 6 months. Further follow-up is ongoing.

1.2.1.3 Safety Profile[20]

At the time of the study-specific data cutoff dates, 893 subjects have received talimogene laherparepvec (with doses from 10^4 to 10^8 PFU/mL) and have provided safety data across 15 studies. Thirty-one of these subjects continued into the extension phase of 2 of these studies. Overall, most adverse events reported in subjects administered talimogene laherparepvec are non-serious and primarily include flu-like symptoms and injection site reactions. Most fatal adverse events reported in subjects administered talimogene laherparepvec were reported in the setting of disease progression.

Table 1.2.1.3 Adverse Reactions Observed in Imlygic Clinical Trials

ADRs are displayed by MedDRA SOC, PT and frequency in the Imlygic arm using the following convention: very common (≥ 1/10); common (≥1/1,000 to < 1/100); rare (≥ 1/10,000 to 1/1,000); very rare (< 1/10,000).

		Imiygic (N= 292)			
			Events with Severity		
System Organ Class Preferred Term	CIOMS Frequency	All Events n (%)	Grade 3-4 n (%)	Grade 5 n (%)	Serious Events n (%)
Number of Subjects reporting treatment-emergent adverse events	Very Common	290 (99.3)	94 (32.2)	11 (3.8)	75 (25.7)
Infections and Infestations					
Cellulitis	Common	17 (5.8)	6 (2.1)	0 (0)	7 (2.4)
Oral herpes	Common	14 (4.8)	0 (0)	0 (0)	0 (0)
Incision site infection	Uncommon	2 (<1)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Tumour pain	Common	22 (7.5)	5 (1.7)	0 (0)	4 (1.4)
Infected neoplasm	Common	8 (2.7)	3 (1.0)	0 (0)	3 (1.0)
Plasmacytoma[1]	Uncommon	1 (<1)	1 (<1)	0 (0)	1 (<1)
Blood and lymphatic system disorders					
Anaemia	Common	15 (5.1)	3 (1.0)	0 (0)	2 (<1)
Immune system disorders					
Glomerulonephritis	Uncommon	1 (<1)	1 (<1)	0 (0)	1 (<1)
Pneumonitis[2]	Uncommon	1 (<1)	1 (<1)	0 (0)	0 (0)
Psoriasis[3]	Uncommon	1 (<1)	1 (<1)	0 (0)	0 (0)
Vasculitis	Uncommon	1 (<1)	0 (0)	0 (0)	0 (0)
Metabolism and nutrition disorders					
Dehydration	Common	12 (4.1)	5 (1.7)	0 (0)	2 (<1)
Nervous system disorders					
Headache	Very Common	55 (18.8)	2 (<1)	0 (0)	0 (0)
Dizziness	Common	28 (9.6)	0 (0)	0 (0)	0 (0)
Eye disorders					
Keratitis herpetic	Uncommon	1 (<1)	0 (0)	0 (0)	0 (0)
Vascular disorders					
Flushing	Common	11 (3.8)	0 (0)	0 (0)	0 (0)
Deep vein thrombosis	Common	6 (2.1)	5 (1.7)	0 (0)	3 (1.0)
Respiratory, thoracic and mediastinal disorders					
Oropharyngeal pain	Common	17 (5.8)	0 (0)	0 (0)	0 (0)
Obstructive airways disorder	Uncommon	1 (<1)	1 (<1)	0 (0)	1 (<1)
Gastrointestinal disorders					
Nausea	Very Common	104 (35.6)	1 (<1)	0 (0)	0 (0)
Vomiting	Very Common	62 (21.2)	5 (1.7)	0 (0)	2 (<1)
Diarrhoea	Very Common	55 (18.8)	1 (<1)	0 (0)	0 (0)
Constipation	Very Common	34 (11.6)	0 (0)	0 (0)	2 (<1)
Abdominal pain	Common	26 (8.9)	3 (1.0)	0 (0)	0 (0)
Abdominal discomfort	Common	6 (2.1)	0 (0)	0 (0)	0 (0)
Skin and subcutaneous tissue disorders					
Rash	Common	26 (8.9)	1 (<1)	0 (0)	0 (0)
Vitiligo	Common	15 (5.1)	0 (0)	0 (0)	0 (0)
Dermatitis	Common	5 (1.7)	0 (0)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders					
Myalgia	Very Common	51 (17.5)	1 (<1)	0 (0)	0 (0)
Arthralgia	Very Common	50 (17.1)	2 (<1)	0 (0)	0 (0)
Pain in extremity	Very Common	48 (16.4)	4 (1.4)	0 (0)	0 (0)
Groin pain	Common	10 (3.4)	0 (0)	0 (0)	0 (0)

General disorders and administration site conditions					
Fatigue	Very Common	147 (50.3)	5 (1.7)	0 (0)	0 (0)
Chills	Very Common	142 (48.6)	0 (0)	0 (0)	1 (<1)
Pyrexia	Very Common	125 (42.8)	0 (0)	0 (0)	5 (1.7)
Injection site reactions[4]	Very Common	115 (39.4)	3 (1.0)	0 (0)	0 (0)
Influenza like illness	Very Common	89 (30.5)	2 (<1)	0 (0)	1 (<1)
Malaise	Common	12 (4.1)	0 (0)	0 (0)	0 (0)
Axillary pain	Common	10 (3.4)	0 (0)	0 (0)	0 (0)
Investigations					
Weight decreased	Common	17 (5.8)	1 (<1)	0 (0)	0 (0)
Injury, poisoning and procedural complications					
Contusion	Common	14 (4.8)	0 (0)	0 (0)	0 (0)
Procedural pain	Common	9 (3.1)	1 (<1)	0 (0)	1 (<1)
Wound complication	Common	4 (1.4)	0 (0)	0 (0)	0 (0)
Wound secretion	Common	4 (1.4)	0 (0)	0 (0)	0 (0)

Adverse events were coded using MedDRA version 15.1.
Adverse Reactions were defined as: adverse events with >= 2% more frequent incidence in Imlygic-treated patients compared to GM-CSF-treated patients in Study 1 OR adverse events with less than 2% difference, but with a biologically plausible mechanism and similar in medical concept to other adverse events.
The classification of Very common, Common and Uncommon events is based on cutoff percentages that were applied to adverse event incidence in the "All Events" column of the Imlygic arm.
1 Plasmacytoma at the injection site.
2 Pneumonitis is considered an immune mediated event and is therefore categorized with the other adverse events in the system organ class of Immune system disorders.
3 Worsening psoriasis.
4 Injection Site Reactions includes Injection site pain, Injection site erythema, Injection site haemorrhage, Injection site swelling, Injection site reaction, Injection site inflammation, Secretion discharge, Injection site discharge, Injection site warmth.

Important Identified Risks[20]

- Disseminated herpetic infection in severely immunocompromised individuals (those with any sever congenital or acquired cellular and/or humoral immune deficiency).
- Accidental exposure of healthcare providers to talimogene laherparepvec.
- Obstructive airway disorder.
- Immune-mediated adverse events.
- Plasmacytoma at the injection site.
- Deep vein thrombosis
- Cellulitis at site of injection.
- SCCHN Indication: Arterial Bleeding (Carotid Artery Blowout Syndrome).

Important Potential Risks[20]

- Disseminated herpetic infection in immunocompromised patients (such as those with human immunodeficiency virus [HIV]/acquired immunodeficiency syndrome [AIDS], leukemia, lymphoma, common variable immunodeficiency, or those who require high-dose steroids or other immunosuppressive agents).
- Symptomatic talimogene laherparepvec infection in non-tumor tissue in treated patients.
- Transmission of talimogene laherparepvec from patient to close contacts or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation).

- Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type HSV-1 in patients.
- Combination with other therapies like chemotherapy or immunosuppressive agents.
- Recombination of talimogene laherparepvec with wild-type HSV-1 virus may occur.
- Impaired wound healing at site of injection.
- Delayed next line treatment in non-responders.
- Loss of efficacy in patients treated with systemic acyclovir for complications.
- Talimogene laherparepvec-mediated anti-GM-CSF antibody response.

1.2.1.4 Special Warning and Precautions for Use

Immunocompromised Patients
Talimogene laherparepvec has not been studied in immunocompromised patients. Based on animal data, patients who are severely immunocompromised may be at an increased risk of disseminated herpetic infection and should not be treated with talimogene laherparepvec. Disseminated herpetic infection may also occur in immunocompromised patients (such as those with HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency, or who require chronic high-dose steroids or other immunosuppressive agents). Consider the risks and benefits of treatment before administering talimogene laherparepvec to these patients.

Accidental Exposure to TVEC
Accidental exposure may lead to transmission of talimogene laherparepvec and herpetic infection. Healthcare providers, close contacts (household members, caregivers, sex partners, or persons sharing the same bed), pregnant women, and neonates should avoid direct contact with injected lesions or body fluids of treated patients. Accidental needle stick and splash back have been reported in healthcare providers during preparation and administration of talimogene laherparepvec.

Patients should be advised to avoid touching or scratching injection sties as this could lead to inadvertent transfer of Imlygic to other areas of their body. Close contacts who are pregnant or immunocompromised should not change the patient's dressings or clean their injection sites.

Caregivers should be advised to wear protective gloves when assisting patients in applying or changing occlusive dressings and observe safety precautions for disposal of used dressings and cleaning materials.

In the event of an accidental exposure to talimogene laherparepvec, exposed individuals should be advised to clean affected area thoroughly with soap and water and/or a disinfectant. If signs or symptoms of herpetic infection develop, they should contact their healthcare provider. Talimogene laherparepvec is sensitive to acyclovir.

Herpetic Infection in TVEC-treated Patients
In clinical studies, herpetic infections (including cold sores and herpes keratitis) have been reported in patients treated with talimogene laherparepvec. Patients who develop herpetic infections should be advised to follow standard hygienic practices to prevent viral transmission. Talimogene laherparepvec is sensitive to acyclovir. Consider the risks and benefits of talimogene laherparepvec treatment before administering acyclovir or other anti-viral agents indicated for management of herpetic infection. These agents may interfere with the effectiveness of talimogene laherparepvec.

Cellulitis at the Injection Site
Necrosis or ulceration of tumor tissue may occur during talimogene laherparepvec treatment. Cellulitis and systemic bacterial infection have been reported. Careful wound care and infection precautions are recommended, particularly if tissue necrosis results in open wounds.

Immune-mediated Events
In clinical studies, immune-mediated events including glomerulonephritis, vasculitis, pneumonitis, worsening psoriasis, and vitiligo have been reported in patients treated with talimogene laherparepvec.

Plasmacytoma at the Injection Site
Plasmacytoma has been reported in proximity to the injection site after administration of talimogene laherparepvec. Consider the risks and benefits of talimogene laherparepvec in patients with multiple myeloma or in whom plasmacytoma develops during treatment.

Obstructive Airway Disorder
Obstructive airway disorder has been reported following talimogene laherparepvec treatment. Use caution when injecting lesions close to major airways.

Arterial Bleeding (Carotid Artery Blowout Syndrome)
Fatal carotid arterial bleeding (carotid blowout syndrome) has been reported following administration of talimogene laherparepvec in the squamous cell carcinoma of the head and neck (SCCHN) setting. Subjects with tumor(s) in direct contact or encasing a major blood vessel, ulceration and/or fungation onto the skin surface, and subjects with history of re-irradiation for SCCHN or prior lymph node neck dissection may be at increased risk for arterial bleeding if talimogene laherparepvec is injected into a tumor located near a major blood vessel. Such high risk subjects should not be administered talimogene laherparepvec in the SCCHN setting.

1.3 Study Rationale

The overall goal of this phase I trial is to exploit the oncolytic and immune-stimulating properties of talimogene laherparepvec to develop a new therapeutic approach to human peritoneal surface dissemination of gastrointestinal, fallopian tube, ovarian, and primary peritoneal cancers. As an exploratory endpoint, we will evaluate the impact of talimogene laherparepvec on peritoneal leukocyte populations of patients with peritoneal surface malignancies. We hope to set the stage for future clinical trials by evaluating the safety of intraperitoneal delivery of talimogene laherparepvec to patients who cannot undergo complete cytoreductive surgery for peritoneal surface dissemination of gastrointestinal, fallopian tube, ovarian or primary peritoneal malignancies.

2.0 OBJECTIVES

2.1 Primary Objective

The primary objective of this trial is:

1. To evaluate the toxicity profile of intraperitoneal talimogene laherparepvec in patients with peritoneal surface dissemination from gastrointestinal, fallopian tube, ovarian, or primary peritoneal tumors.

2.2 Secondary Objectives

The secondary objective of this trial is:

1. To evaluate the pharmacokinetic profile and viral shedding of talimogene laherparepvec by measuring viral load in plasma and urine as well as viral load in peritoneal fluid.

2.3 Exploratory Objectives

The exploratory objectives of this trial are:

1. To evaluate the magnitude and duration of tumor response.
2. To evaluate the time to tumor progression as measured by radiographic imaging, clinical symptoms, and/or tumor marker levels.
3. To describe the clinical activity of talimogene laherparepvec, as measured by overall survival.
4. To evaluate the changes in peritoneal cavity leukocyte populations after the treatment of peritoneal surface dissemination of gastrointestinal, fallopian tube, ovarian, and primary peritoneal cancers with talimogene laherparepvec.

3.0 STUDY DESIGN

3.1 Study Description

This is a non-randomized, open-label Phase I trial in patients with Stage IV peritoneal surface dissemination from gastrointestinal, fallopian tube, ovarian, or primary peritoneal tumors enrolled at Duke Cancer Institute and select external collaborating institutions. All subjects will complete an extensive medical history, baseline physical examination and clinical assessment to ensure subject eligibility requirements (see Eligibility Criteria for details) within 4 weeks of starting study drug. All eligible patients must have a peritoneal catheter placed prior to the initiation of therapy. All patients will receive an initial seroconversion dose of talimogene laherparepvec $4x10^6$ PFU on Cycle 1 Day 1 to enable seroconversion as described in the currently approved treatment protocol for the treatment of cutaneous melanoma. Three weeks (+3 days) after the initial seroconversion dose, patients will receive talimogene laherparepvec at the dose level for the cohort for which they are enrolled every 2 weeks (±3 days) for up to 4 doses. The length of the first cycle is 5 weeks and subsequent cycles are 2 weeks in duration.

- Enrolled subjects are defined as subjects who give informed consent.
- Screen failures are defined as subjects who give informed consent and do not meet eligibility criteria.
- Accrued subjects are defined as subjects who give informed consent and meet eligibility criteria.
    - Withdrawal: Subject accrued but later withdrawn from the study, either before or after receiving a study drug.
    - Evaluable: In the Dose Escalation Cohort, subjects who are accrued, received study treatment, and completed the first cycle of safety assessments or have dose limiting toxicity (DLT) which is study treatment related that precludes completing the full cycle of assessments will be considered evaluable for DLT. All subjects (in Dose Escalation and Dose Expansion) who are accrued and receive any study treatment will be considered evaluable for toxicity. All subjects in Dose Escalation and Dose Expansion who are accrued and receive any study treatment will be considered evaluable for efficacy.
    - Non-evaluable: In the Dose Escalation Cohort, subjects who accrued but did not complete the first cycle of safety assessments due to reasons other than study treatment-

related toxicity (e.g. disease progression or inter-current illness) are considered non-evaluable for DLT. All subjects (in Dose Escalation and Dose Expansion) who are accrued, received study treatment but did not complete initial restaging due to reasons other than disease progression (e.g. inter-current illness) will be considered non-evaluable for efficacy.

Table 3.1 Proposed Dose Levels

Dose Level	No. Evaluable Subjects	TVEC IP, once every 2 weeks x 4 doses*
Dose Escalation		
1 (starting dose)	3-6	$4x10^6$
2	3-6	$4x10^7$
3	3-6	$4x10^8$
Dose Expansion		
Expanded Cohort	6	MTD

*All patients will receive an initial seroconversion dose of $4x10^6$ PFU. The first dose at each of these Dose Levels will be administered 3 weeks (+3 days) after the initial seroconversion dose, and then be given every 2 weeks ± 3 days for a total of 4 doses at each Dose Level (in addition to the initial seroconversion dose, which all patients will receive).

Using a standard '3+3' dose escalation design, there are up to three dose levels that may be explored. See Table 3.1 for the dosing scheme.

3.2 Dose Escalation

The first portion of the study will evaluate the toxicity profile of talimogene laherparepvec in patients with peritoneal surface dissemination from gastrointestinal, fallopian tube, ovarian, or primary peritoneal tumors.

Using a standard '3+3' dose escalation design, there are up to three dose levels that may be explored. Dose escalation will be dependent on dose-limiting toxicity (DLT) within the cohorts. The following are guidelines for dose escalation:

- Three (3) subjects will be accrued at the starting dose level. Subjects will be monitored for the first cycle (ie. first 5 weeks) before advancement to the next dose level. If no DLTs are seen, 3 subjects may be enrolled to the next dose level.
- If 1 of 3 subjects has a DLT at any dose level, then up to an additional 3 subjects will be enrolled at that dose level. If 1 of 6 subjects experience DLT at a given dose level, then escalation may continue to the next dose level.
- If 2 or more out of 3-6 subjects have DLT in any dose level, then that dose level will be considered to have unacceptable toxicity and the next lower dose level will have additional subjects enrolled to expand to 6 subjects. In this case, the next lower dose level will be declared as the MTD provided no more than 2 of 6 subjects have DLT.
- After the first dose level has completed enrollment, all enrolled subjects will complete at least the first 5 weeks of safety assessments. At that point, the PI, co-PI, and study chair will meet to review safety data for DLTs and determine whether enrollment can proceed at the next dose level. They will notify the funding company of the outcome of the meeting.
- In cases where the only toxicity seen at the lower dose level is Grade ≤ 2, re-escalation for intermediate dosing will be considered.

- If there is uncertainty about study drug attribution to DLT, then re-escalation to the next dose level is permitted.
- If ≥ 33% of subjects has DLT at any dose level, then that dose level will be considered to have unacceptable toxicity. The dose level immediately below the one with unacceptable toxicity will be MTD, provided that at least 6 patients have been enrolled to the lower dose level and it was deemed safe.
- If no unacceptable toxicity is seen at the highest dose level, then the highest dose level will be considered the MTD.
- Up to 6 subjects will be enrolled at MTD before proceeding to the Dose Expansion Cohort.
- Once the MTD/RPTD has been determined, the next stage of the study is the Dose Expansion Cohort.

3.2.1 Dose Limiting Toxicity

Toxicity should be evaluated and defined according to CTCAE version 5.0, and should only include events assessed as related to talimogene laherparepvec during treatment and up to 30 days after the last talimogene laherparepvec injection.

The following herpetic events should be considered as DLTs:

- Serious herpetic events such as herpetic encephalitis, encephalomyelitis or disseminated hepatic infection.
- Any herpetic events confirmed due to talimogene laherparepvec that require treatment with acyclovir or similar anti-viral agent. Talimogene laherparepvec treatment should be suspended if treatment is required with systemic acyclovir or other anti-virals. If ongoing anti-viral treatment is required, talimogene laherparepvec treatment should be permanently discontinued.

The following are also considered DLTs:

- Grade 3 or greater immune-mediated adverse events.
- Any grade plasmacytoma at or near the injection site or evidence of impaired wound healing at the injection site.
- Grade 3 or greater allergic reactions considered at least possibly related to talimogene laherparepvec.
- Grade 4 non-hematologic toxicity.
- Grade 3 non-hematologic toxicity lasting > 3 days despite optimal supportive care;
    - Grade 3 fatigue will not be classified as DLT, irrespective of duration.
- Any Grade 3 or higher non-hematologic laboratory value if:
    - Medical intervention is required, or
    - The abnormality leads to hospitalization, or
    - The abnormality persists for > 1 week unless deemed not clinically important per both treating physician and study PI or co-PI.
- Grade 3 or 4 febrile neutropenia.
- Grade 4 thrombocytopenia associated with bleeding event required intervention.
- Any other intolerable toxicity leading to permanent discontinuation of talimogene laherparepvec.
- Grade 5 toxicity (i.e., death).

If an unexpected DLT occurs, talimogene laherparepvec administration should be delayed until the DLT has resolved to at least CTCAE (v. 5.0) Grade 1. If talimogene laherparepvec dosing is delayed by more than 6 weeks from the date of the planned dose due to the occurrence of an adverse event that is

considered related to talimogene laherparepvec, the subject must be permanently taken off talimogene laherparepvec treatment.

Management and dose modifications associated with all adverse events are outlined in Section 7.0.

3.3 Dose Expansion Cohort

Once the MTD has been determined, an additional 6 subjects will be enrolled to the dose expansion cohort. All subjects will receive an initial seroconversion dose of talimogene laherparepvec $4x10^6$ PFU on Cycle 1 Day 1. Three weeks (+3 days) after the initial seroconversion dose, patients will receive talimogene laherparepvec at the MTD every 2 weeks (±3 days) for up to 4 doses (in addition to the initial seroconversion dose, which all patients will receive). The length of the first cycle is 5 weeks and the subsequent cycles are 2 weeks in duration. There are a total of four cycles.

4.0 SUBJECT SELECTION

4.1 Inclusion Criteria

1. Patients must have stage IV peritoneal surface dissemination of gastrointestinal cancer or recurrent ovarian, fallopian tube or primary peritoneal cancer with metastatic disease to the peritoneum that cannot be completely resected at time of abdominal exploration. Please note:
    a. Locoregional extension of peritoneal disease beyond the peritoneal cavity (including but not limited to the pleura and subcutaneous soft tissue) is permitted with PI approval,
    b. Radiographically measurable disease per RECIST 1.1 is preferable, but for patients with previously documented gastrointestinal, fallopian tube, ovarian, or primary peritoneal cancer, for whom relevant tumor markers (including but not limited to CEA, CA 19-9 or CA-125) have been useful markers of disease progression and/or response to treatment, an elevated relevant tumor marker (including but not limited to CEA, CA 19-9 or CA-125) above the institutional upper limit of normal could be substituted for radiographic imaging,
    c. Asymptomatic primary tumors are permitted.
2. Subjects must have had at least one prior round of systemic therapy in the metastatic setting or have refused or be ineligible for standard systemic therapy for their disease type. No prior systemic therapy is required for low grade mucinous cancers.
3. Age ≥ 18 years
4. ECOG Performance Score of 0-2
5. Adequate marrow function as evidenced by:
    a. Absolute neutrophil count (ANC) ≥ 1,500/μL
    b. Platelets ≥ 100,000/μL
    c. Hemoglobin (Hgb) ≥ 8 g/dL
6. Adequate renal function as evidenced by serum creatinine ≤ 1.5 x upper limit of normal (ULN), OR 24-hour creatinine clearance ≥ 60 mL/min for subject with creatinine levels > 1.5 x ULN.
7. Adequate hepatic function as evidenced by:
    a. Serum bilirubin ≤ 1.5 x ULN OR direct bilirubin ≤ ULN for a subject with total bilirubin level > 1.5 x ULN
    b. Aspartate aminotransferase (AST) ≤ 3 x ULN
    c. Alanine aminotransferase (ALT) ≤ 3 x ULN
    d. Alkaline phosphatase ≤ 3 x ULN
8. 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 (and may need to be held per institutional standards for placement of the Bard peritoneal catheter).

9. Patients must be recovered from both acute and late effects of any prior surgery, radiotherapy or other antineoplastic therapy.
10. Patients of reproductive potential (men and women) must agree to use medically accepted barrier methods of contraception (e.g., male or female condom) at the time of pregnancy test (women of childbearing potential only), during the course of the study and for 90 days after the last dose of study drug, even if oral contraceptives are also used. All subjects of reproductive potential must agree to use both a barrier method and a second method of birth control during the course of study and for 90 days after the last dose of study drug.
11. Patients or their legal representatives must be able to read, understand and provide informed consent to participate in the trial.

4.2 Exclusion Criteria

1. Prior chemotherapy, radiotherapy, biological cancer therapy, targeted therapy, or major surgery within 28 days prior to enrollment or has not recovered to CTCAE grade 1 or better from adverse event due to cancer therapy administered more than 28 days prior to enrollment. (Exception: Patients with peripheral neuropathy < Grade 3 are eligible)
2. Patients who received radiotherapy to more than 25% of their bone marrow.
3. Currently receiving treatment with another investigational device or drug study, or < 30 days since ending treatment with another investigational device or drug study(s). Other investigational procedures while participating in this study are excluded.
4. Known active central nervous system (CNS) metastases. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids >10 mg/day of prednisone or equivalent. The exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.
5. Metastatic disease in a site other than the peritoneal surfaces. Note: Locoregional extension of peritoneal disease may be permitted with PI approval.
6. History or evidence of active autoimmune disease for which subject currently requires systemic treatment (i.e., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
7. Evidence of clinically significant immunosuppression such as the following:
    a. Primary immunodeficiency state such as Severe Combined Immunodeficiency Disease.
    b. Concurrent opportunistic infection.
    c. Receiving systemic immunosuppressive therapy (> 2 weeks) including oral steroid doses >10mg/day of prednisone or equivalent within 7 days prior to enrollment.
8. History of allogenic organ or hematopoietic transplant.
9. Active HSV that requires intermittent or chronic systemic anti-herpetic therapy or prior complications of herpetic infection, e.g. herpetic keratitis or encephalitis.
10. Requiring intermittent or chronic systemic (intravenous or oral) treatment with an antiherpetic drug (e.g., acyclovir), other than intermittent topical use.
11. Prior treatment with talimogene laherparepvec or any other oncolytic virus.

12. Subject has known sensitivity to talimogene laherparepvec or any of its components to be administered during dosing.
13. Prior therapy with tumor vaccine.
14. Receipt of a live vaccine within 28 days prior to enrollment.
15. Known to have acute or chronic active hepatitis B or C infection (active, previously treated, or both).
16. Known history of HIV infection.
17. Active infection or fever ≥ 101.3°F.within 3 days of port placement. .
18. Bleeding disorders that would preclude intraperitoneal port placement.
19. Refractory ascites that requires palliative paracentesis more frequently than once a month. Any other medical condition, including mental illness or substance abuse, deemed by the Investigator to be likely to interfere with a patient's ability to sign informed consent, cooperate and participate in the study or interferes with the interpretation of the results.
20. History of other malignancy within the past 5 years.
21. Female subjects who are pregnant or breast-feeding, or planning to become pregnant during study treatment or through 90 days after the last dose of talimogene laherparepvec.
22. Subjects of childbearing potential who are unwilling to use acceptable method(s) of effective contraception during study treatment and through 90 days after the last dose of talimogene laherparepvec.
23. Sexually active subjects and their partners unwilling to use male or female latex condom to avoid potential viral transmission during sexual contact while on treatment and within 90 days after treatment with talimogene laherparepvec.

4.3 Inclusion of Women and Minorities

Men and women of all races and ethnic groups are eligible for this trial.

5.0 STUDY ASSESSMENTS

Note: After Cycle 1, if the subject is unable to have a study assessment taken within the defined time window due to an event outside of his or her control (e.g., clinic closure, personal emergency, inclement weather, vacation), the assessment should be performed as close as possible to the required schedule.

Refer to **Appendix** C for **Study Calendar**.

5.1 Screening Period

During the Screening Period, subjects are consented and screened for the study. Informed consent must be obtained before initiation of any screening procedure that is performed solely for the purpose of determining eligibility for this study. Evaluations performed as part of routine care before informed consent can be considered as screening evaluations if done within the defined screening period, and if permitted by the local Institutional Review Board (IRB) / Independent Ethics Committee (IEC) policies. Study eligibility is based on meeting all of the inclusion criteria and none of the exclusion criteria (refer to Section 4.0) before the first dose of study drug on Cycle 1 Day 1.

The following study procedures must be done within 28 days prior to Cycle 1 Day 1:

- Demographics
- Medical and cancer history
- Concomitant medications
- Physical examination
- Abdominal measurement
- Height
- Vital signs and weight
- ECOG performance status
- Adverse event assessment (review of baseline symptoms)
- Tumor assessment (CT and/or MRI scans)
- Blood tumor marker, if clinically indicated (e.g., CEA or CA19-9)
- Whole blood (for pharmacogenomics) (may be collected pre-dose on Cycle 1 Day 1)
- Coagulation tests (must be done prior to catheter placement)
- Peritoneal catheter placement (must be placed after confirmation of eligibility)

The following study procedures must be done within 7 days prior to Cycle 1 Day 1:

- CBC with differential
- Chemistries including liver function tests (LFTs)
- Serum pregnancy test (only for women of childbearing potential)

Subject eligibility is determined using lab results obtained prior to peritoneal port placement and up to 7 days prior to Cycle 1 Day 1. The Screening Period ends upon placement of the peritoneal port or final determination that the subject is ineligible for the study. Patients with pre-existing peritoneal ports for standard of care treatment are eligibile for participation. For these patients the Screening Period ends upon receipt of the first dose of study drug or final determination that the subject is ineligible for the study.

5.2 Peritoneal Catheter Placement

After confirmation of patient eligibility, the peritoneal catheter must be placed prior to initiation of treatment. Catheter placement must occur on Day -4 (+/- 2 days) prior to C1D1.

5.3 Treatment Period

During the Treatment Period, subjects will receive an initial seroconversion dose of talimogene laherparepvec on Day 1 of Cycle 1. Three weeks (±3 days) after the initial seroconversion dose, patients will receive talimogene laherparepvec at their designated dose level every 2 weeks (± 3 days) for up to four doses or until either: 1) the occurrence of unacceptable treatment-related toxicity; or 2) other reason(s) for subject discontinuation as described in Section 5.7.

All subjects will have study procedures weekly during the first cycle, then Day 1 of each cycle. After the completion of the first cycle, laboratory assessments may be obtained up to 3 days prior to Day 1. If clinically indicated, additional visits and/or safety assessments may be warranted.

The following study procedures must be completed on **Day 1 of each cycle**:

- Physical examination
- Abdominal measurement
- Vital signs (q15 min x 1 hour and again after additional hour of observation)

- Weight
- Concomitant medications
- ECOG performance status
- Adverse event assessment
- CBC with differential (results from eligibility review on day -7 to -3 should be used for C1D1)
- Chemistries including LFTs (results from eligibility review on day -7 to -3 should be used for C1D1)
- Viral load (prior to treatment D1 of each cycle)
- Urine pregnancy test prior to each treatment (only for women of childbearing potential)
- Peritoneal Cytokines (prior to treatment on C2D1 and C4D1)
- Immune cells (prior to treatment on C2D1 and C4D1)
- Plasma (prior to treatment D1 of each cycle)

The following study procedures must be completed on **Days 8, 15 and 29 of Cycle 1**:

- Physical examination
- Vital signs and weight
- Concomitant medications
- ECOG performance status
- Adverse event assessment
- CBC with differential
- Chemistries including LFTs
- Viral load

The following study procedures must be completed **on Cycle 1 Day 22**:

- Physical examination
- Vital signs (q15 min x 1 hour and again after additional hour of observation)
- Weight
- ECOG performance status
- CBC with differential
- Chemistries including LFTs
- Viral load (prior to treatment)
- Plasma (prior to treatment)

The following study procedures must be completed **at C4D1 (+/-3 days)**:

- Concomitant medications
- Adverse event assessments
- Peritoneal cytokines (prior to treatment)
- Immune cells (prior to treatment)
- Plasma
- Viral load (prior to treatment)

The following study procedures must be completed **at C4D14 (+/-3 days):**

- Tumor assessment (CT and/or MRI scans)
- Blood tumor marker, if clinically indicated (e.g., CEA or CA19-9)

Restaging scans will be performed at C4D14 (+/- 3 days) on study treatment and disease response will be assessed using guidelines described in Section 5.6.

The Treatment Period ends when a subject receives his or her last dose of study treatment; the subject then enters the Follow-up Period.

5.4 Follow-up Period

Subjects should return 30 (±7) days after their last dose of study drug for an off-treatment visit to complete the following study procedures:

- Physical examination
- Abdominal measurement
- Vital signs and weight
- Concomitant medications
- ECOG performance status
- Adverse event assessment
- CBC with differential
- Chemistries including LFTs
- Serum pregnancy test (only for women of childbearing potential)
- Viral load (at disease progression and 30 day off treatment follow up)
- Peritoneal cytokines (at disease progression or off treatment, and 30 day off treatment follow up)
- Immune cells (at disease progression or off treatment, and 30 day off treatment follow up)
- Plasma (at disease progression or off treatment)

At the time of the follow up visit, the treating physician can determine whether or not to remove the IP catheter. If they anticipate using it for other IP therapies, it can be left in. If catheter is removed, treating physician may also determine whether it is clinically indicated to do PT/PTT. Additional follow-up may occur for subjects with adverse events (AEs) related to study drug that are ongoing at the time of this off-treatment visit unless AE is deemed unresolvable or subject has started a new anti-cancer treatment regimen.

For long-term follow up, subjects will be followed for progression every 12 weeks or as indicated until disease progression or start of new anti-cancer therapy. For subjects that complete or discontinue treatment without documented disease progression, subjects will have disease status (blood tumor marker(s) and restaging scans with RECIST 1.1 evaluation every 12 weeks) followed until disease progression or start of new anti-cancer treatment regimen.

All subjects will be followed for survival for up to 1 year after completing treatment. Survival status may be collected by personal interviews or review of medical records.

5.5 Laboratory Assessments

Local laboratories will perform all clinical laboratory tests using standard procedures, and results will be provided to the Investigator. Abnormalities in clinical laboratory tests that lead to a change in subject management (e.g., requirement for additional medication, treatment or monitoring) are considered clinically significant for the purposes of this study, and will be recorded on the case report form (CRF). If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as a serious adverse event (SAE).

Refer to Appendix D for details of laboratory tests for this study. In addition, blood tumor markers (if clinically indicated) such as CEA and/or CA19-9, will be obtained at baseline and at every restaging.

5.6 Adverse Event Assessment

AE definition is described in Section 10.1. AEs will be documented throughout the study. AE seriousness, grade, and relationship to study drug will be assessed by the Investigator using NCI-CTCAE version 5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf).

SAE definitions and reporting requirements are described in Section 10.2.

Select non-serious and serious adverse events also known as Events of Clinical Interest (ECI) must be recorded and reported as described in Section 10.3.

5.7 Tumor Assessments

Tumor Response will be assessed via a composite of a variety of endpoints and ultimately, the treating physician's judgment and assessment of these endpoints. Given the variability in clinical presentation of these malignancies, radiographic imaging findings, and baseline laboratory values, assessing tumor response may take into account clinical features, radiographic response, laboratory response, and clinical endpoints.

Clinical features may include, but are not limited to, performance status (ECOG or Karnofsky score), abdominal girth, development of bowel obstructions felt to be resulting from peritoneal tumor deposits, development of clinically-evident ascites, and frequency of paracenteses due to malignant ascites.

Radiographic response may be used to track those patients who have radiographically-evaluable tumor deposits at baseline, which may be prone to following with serial imaging. For a subset of these patients who have such radiographically-evaluable lesions, it may be possible to assess tumor response based on serial imaging (CT chest/abdomen/pelvis with and without contrast and/or MRI or PET imaging), using RECIST version 1.1 criteria. Some peritoneal surface malignancies will not be amenable to grading using RECIST version 1.1 criteria. However, there are other imaging scoring systems such as the SPAAT[11] Score or a modified peritoneal cancer index based upon multi-detector CT imaging [12] which may be helpful in establishing a radiographic determination of tumor response to therapy. The exact method of analyzing a given patient's imaging will depend on that patient's radiographic findings at baseline, and the radiologist's determination of the best method of following serial changes in imaging.

For those patients who have elevated blood tumor markers at baseline, following the response of these tumor markers to therapy will factor into assessing tumor response to therapy.

Clinical endpoints of progression-free survival and overall survival will also be used to assess response to therapy.

Given the heterogeneity in presentations of patients with peritoneal surface malignancies, patients will likely be followed by a composite of a variety of the above endpoints, and these endpoints may be different from patient to patient. However, for a given patient, all attempts will be made to use the same method for tumor assessment at every assessment timepoint. Progressive disease (PD) may manifest in findings such as significant clinical progression, evidence of 20% increase in disease seen on

imaging, and or increase in tumor marker by 20% over baseline. Response may manifest in findings such as improvement in clinical symptoms, evidence of 30% decrease in measurable tumor burden, and/or 30% decrease in tumor marker from baseline.

5.7.1 RECIST version 1.1

RECIST is a set of published rules that define when cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progression") during treatments. The original criteria were published in February 2000 by an international collaboration including the European Organization for Research and Treatment of Cancer (EORTC), National Cancer Institute (NCI) of the United States and the National Cancer Institute of Canada Clinical Trials Group. RECIST 1.1, published in January 2009, is an update to the original criteria and will be used for this study.

Refer to Appendix A for definition of target lesions, methods of measurement and all other related criteria for RECIST version 1.1. The following summarizes the definitions of the criteria used to determine objective tumor response for target lesions:

- **Complete Response (CR)**: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- **Partial Response (PR)**: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD)**: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- **Stable Disease (SD)**: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

5.8 Subject Discontinuation

Subjects will receive study treatment for up to four cycles (after the initial seroconversion dose) or until treatment discontinuation for one of the reasons listed below. However, subjects may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice. All reasons for discontinuation or withdrawal from trial will be recorded.

Reasons for subject discontinuation by the Investigator may include, but are not limited to, the following:

- Death
- Confirmed radiographic disease progression (Note: With approval of the Lead PI, a subject may be granted an exception to continue on study treatment with confirmed radiographic progression if clinically stable or clinically improved.)
- Significant noncompliance by subject or Investigator
- Investigator or Lead PI determination that it is no longer safe and/or no longer in the subject's best interest to continue participation
- Withdrawal of consent

- Lost to follow-up
- Necessity for treatment with other anticancer treatment prohibited by protocol
- Sexually active subjects who refuse to use medically accepted methods of contraception during the course of the study and for 3 months following the last dose of study drug
- Women who become pregnant or are breast feeding
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol

6.0 STUDY DRUGS

6.1 Treatment Compliance and Study Drug Accountability

The Investigator will maintain accurate records of receipt of study drug, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. At completion of the study, to satisfy regulatory requirements regarding drug accountability, all unused study drug will be reconciled and destroyed in accordance with applicable state and federal regulations.

6.2 Talimogene Laherparepvec

Talimogene laherparepvec (T-VEC) is provided as a sterile frozen liquid in a single-use 2.0 mL cyclic olefin polymer 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 myoinositol added as stabilizers and water for injection.. Each vial is intended for single use only.
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.

The vial caps are color coded to easily distinguish between the 10^6 PFU/mL and 10^8 PFU/mL vial concentrations.

6.2.1 Storage and Handling

Talimogene laherparepvec should be stored protected from light and according to the storage and expiration information (where required) provided on the label that is affixed to the package containing the investigational product. Talimogene laherparepvec should be thawed per the instructions provided in the pharmacy manual. Vials should be checked for cracks or damage that may occur during the thawing process if not performed properly. Drug vials will be destroyed on site once Product complaint has been resolved. See Pharmacy Information Guide.**Special Instructions for Use and Handling**

Follow local institutional guidelines for handling and administration, personal protective equipment, accidental spills, and waste disposal.

- Wear protective gown or laboratory coat, safety glasses, or face shield and gloves while preparing or administering talimogene laherparepvec. Cover any exposed wounds before administering. Avoid contact with skin, eyes or mucous membranes.
- After placement of the IP catheter, there will be a gauze and occlusive dressing placed over the puncture site for 7 days. Replace dressing if it falls off during this time.
- Dispose of all materials that have come in contact with talimogene laherparepvec (e.g., vial, syringe, needle, any cotton or gauze) in accordance with local institutional procedures.
- In the event of an accidental occupational exposure to talimogene laherparepvec (e.g., through a splash to the eyes or mucous membranes) during preparation or administration, flush with clean water for at least 15 minutes. In the event of exposure to broken skin or needle stick, clean the affected area thoroughly with soap and water and/or disinfectant.
- Spills should be treated with a virucidal agent such as 1% sodium hypochlorite or Virkon®. All materials contaminated with talimogene laherparepvec must be disposed of in compliance with local institutional guidelines. Incineration is appropriate.
- Advise subjects to place used dressings and cleaning materials in a sealed plastic bag and dispose in household waste or return to study site depending on local guidance.

The use of a microbiological safety cabinet or hood for the dispensing of talimogene laherparepvec or for talimogene laherparepvec to be drawn up into syringes is not required for 1 mL stoppered vials. As such, it is appropriate to dispense vials of drug such that product is then drawn up into syringes in the room used for product administration, although this may also optionally occur elsewhere (e.g., in the pharmacy).

6.2.2 Administration

All eligible subjects will have a Bard peritoneal catheter placed prior to the initiation of therapy. Talimogene laherparepvec will be administered via intraperitoneal (IP) administration. The planned dose of talimogene laherparepvec (measured as plaque forming units or PFU) will be delivered in a 500 mL volume of normal saline. After the infusion, patient should roll to the right side, wait 10 minutes, then roll to the left side and wait an additional 10 minutes, and repeat this procedure of rolling to the right side and the left side every 10-15 minutes to ensure exposure of the virus to the peritoneal surfaces where disease is located. Patients will have vital signs (blood pressure, pulse, temperature, and respiratory rate) taken every 15 minutes for the first hour after infusion, then remain under observation for an additional hour to ensure no significant toxicity is endured as a result of the administration. At the end of the second hour, vitals should be taken again prior to discharge. This procedure should be repeated each of the 5 potential times that talimogene laherparepvec is administered throughout the course of the study.

6.3 Concomitant Medications/Vaccinations

Concomitant medications will be documented throughout the study. 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 Lead PI.

6.3.1 Acceptable Concomitant Medications

All treatments that the Investigator considers necessary for a subject's welfare may be administered at the discretion of the Investigator in keeping with the local standards of medical care. All concomitant medication received from the date of signed informed consent through 30 days after the last dose of

study drug should be recorded on the CRF including all prescription, over-the-counter (OTC), herbal supplements, and IV medications.

Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject. Otherwise, subjects of reproductive potential must agree to use two birth control methods after informed consent is signed through 90 days after the last dose of study drug. The two methods can either be two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. The following are considered adequate barrier methods of contraception: diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide), cervical cap with spermicide (nulliparous women only), contraceptive sponge (nulliparous women only), and male condom or female condom (cannot be used together). Appropriate hormonal contraceptives will include oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection.

6.3.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Period of this study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than talimogene laherparepvec
- Radiation therapy (Note: Radiation therapy to a symptomatic solitary lesion may be allowed with the approval of the Lead PI.)
- Live vaccines within 30 days prior to the first dose of study drug and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic immunosuppressive therapy within 2 weeks including oral steroid doses > 10 mg/day of prednisone or equivalent within 7 days prior to enrollment.
- Antiherpetic drugs such as acyclovir. Intermittent topical use is permitted.

Subjects who, in the assessment by the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the Investigator deems to be medically necessary.

There are no prohibited therapies during the Follow-up Period.

7.0 DOSE MODIFICATION AND TOXICITY MANAGEMENT

Subjects will be monitored continuously for AEs throughout the study and for 30 days after the last dose of study drug. Subjects will be instructed to notify their treating physician of any and all AEs. Toxicity will be graded according to NCI-CTCAE version 5.0.

All AEs should also be managed with supportive care at the earliest signs of toxicity considered related to study drug(s).

7.1 Dose Modifications

Subjects experiencing one or more AEs due to the study drug may require dose modification(s) as described in Table 7.1. If talimogene laherparepvec treatment was delayed by > 1 week, that dose will be deemed to have been missed and the subject will proceed to the next scheduled treatment visit. Missed doses will not be made up. If talimogene laherparepvec dosing is delayed by more than 4 weeks from the date of the planned dose (i.e., approximately 6 weeks from the previous dose) due to the occurrence of an adverse event that is considered related to talimogene laherparepvec, the subject must be permanently taken off talimogene laherparepvec treatment. If talimogene laherparepvec is delayed by more than 4 weeks from the date of the planned dose (i.e., approximately 6 weeks from the previous dose) for reasons other than treatment-related toxicity, the case must be reviewed by the PI to determine if the subject can resume talimogene laherparepvec therapy.

Table 7.1 Talimogene Laherparepvec Dose Modifications

HEMATOLOGIC ADVERSE EVENTS		
Toxicity Grade[a]	**Occurrence**	**Talimogene laherparepvec**
NEUTROPENIA		
Grade 1	Any	Maintain dose
Grade 2	Any	Maintain dose
Grade 3(≥0.5 - <1x10^9/L)	1st	Hold until grade ≤1, then resume at **current** dose
	2nd and higher	Hold until grade ≤1, then resume at 80% of **current** dose [d]
Grade 4 (< 0.5 x10^9/L)	1st	Hold until grade ≤ 1, then resume at 80% of **current** dose.[b,c,d]
	2nd and higher	Hold until grade ≤1, obtain permission of PI to resume at 60% of **current** dose [d]
FEBRILE NEUTROPENIA		
Grade 3 (neutropenia and fever ≥ 38.5C)	1st – 2nd	Hold until resolution of fever and neutropenia to grade ≤ 1, then resume at 60% of **current** dose [d]
	3rd	Discontinue Protocol Therapy
Grade 4 (neutropenia and fever ≥ 38.5 C)	Any	Discontinue Protocol Therapy

a. National Cancer Institute Common Terminology Criteria Version 3.0
b. Continued treatment only if it is considered to be in the best interest of the patient
c. Consider growth factor support if continuing treatment is felt to be in the patient's best interest.
d. **NOTE:** After Cycle 1, at the discretion of the treating physician, once there is recovery of the toxicity to grade ≤1, the treating physician may choose, to hold oxaliplatin and continue capecitabine and pembrolizumab at current dose as clinically indicated. If the treating physician chooses to restart oxaliplatin later in the patient's treatment course, the dose of oxaliplatin at which the patient restarts should be one dose level lower than last dose level on which patient was treated. The specific treatment approach used and dose modifications that occur are required to be reported in the Case Report Forms.

7.2 Toxicity Management

Talimogene laherparepvec administration can cause side effects, which may include all, some, or none of the following. However, the side effects are not limited to the following lists.

- Very Common side effects (>10% of subjects):
  - Flu-like illness
  - Injection site pain
  - Headache
  - Joint pain
  - Arm or leg pain
  - Diarrhea
  - Constipation
- Common side effects (1-10% of subjects):
  - Injection site reactions
  - Cellulitis
  - Wound complication at the injection site (secretion or discharge)
  - Pain or discomfort
  - Cold sore or fever blister in mouth
  - Anemia
  - Malaise
  - Weight loss
  - Dehydration
  - Bruise
  - Dizziness
  - Flushing
  - Rash
  - Dermatitis
  - Deep vein thrombosis
  - Autoimmune reactions
- Uncommon side effects (less than 1% of subjects):
  - Injection site reactions
  - Herpetic keratitis
  - Angioedema
  - Plasmacytoma
  - Delayed wound healing at the site of injection

Reactions at or near the area of the injection have been seen in other people administered talimogene laherparepvec. Symptoms include bleeding, redness, swelling and inflammation at the injection site. Skin infection caused by bacteria at the site of injection which may require hospitalization for antibiotic treatment have also been reported. Other symptoms may include warmth at the injection site or symptoms of delayed wound healing at or around the injection site such as injection site discharge, foul odor, or dead tissue at the injection site. If you notice symptoms of delayed wound healing at the injection site(s), you should contact the study doctor or his/her staff immediately.

Talimogene laherparepvec contains genetic material that makes human Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF). Known side effects of human GM-CSF include, but are not limited to, musculoskeletal pain, fever, chills, shortness of breath, rash, fatigue, gastrointestinal effects, and fluid around heart and lungs. Although the amount of human GM-CSF released when treating melanoma lesions with talimogene laherparepvec is very small, these side effects may still occur.

Management of any toxicity related to talimogene laherparepvec administration or study may involve holding therapy until patients have recovered from any talimogene laherparepvec- or study-related adverse events. The management of the above known and other toxicity not listed above is largely based upon supportive care and institutional standards in managing these conditions. The management is at the discretion of the treating physician. If deemed appropriate, the treating physician may seek out subspecialty medical care of the patients, e.g. ophthalmologic evaluation for suspected herpetic keratitis, dermatologic consult for skin lesions that need specialist evaluation, or infectious disease consult for suspected herpes infections. Supportive medications may be employed at the discretion of the treating physician to support a patient through symptoms experienced as a result of the toxicity, e.g. pain medications for pain, anti-diarrheal agents for diarrhea, stool softeners and laxatives for constipation, anti-pyretics for fevers, intravenous and oral fluids for dehydration and dizziness, etc. Should a treating physician have any questions about how to treat symptoms related to talimogene laherparepvec or the study, he or she should be encouraged to speak with the PI or co-PI for guidance.

8.0 CORRELATIVES

A key finding in recent years is that treatment with OV initiates inflammation that facilitates cross-presentation of tumor antigens and the induction of local immune responses that are essential for therapeutic efficacy. Recent data demonstrated that OVs activate multiple subsets of dendritic cells (DC) to produce Type I IFN, pro-inflammatory cytokines and T cell co-stimulatory molecules that are key to driving innate and adaptive anti-tumor immune responses. However, limited information is available regarding the role of the immune response in dictating the course of peritoneal carcinomatosis after treatment with OV. In murine models, peritoneal metastatic ovarian and colorectal tumors foster an immunosuppressive, pro-tumor microenvironment that can be skewed toward protective anti-tumor responses using immunomodulatory agents. For example, CT26 peritoneal tumors attracted regulatory T cells (Treg), and treatment with a synthetic TLR7 agonist reduced Treg infiltration and bolstered CD8 T cell-mediated, a tumor-specific immunity[13]. Similarly, immunosuppressive (M2-type) macrophages were re-programmed to a protective M1-type in a peritoneal model of ovarian cancer by treatment with attenuated Listeria monocytogenes, a potent inducer of Th1-type immunity[14]. This is important information, because the immune content of human primary and metastatic CR tumors has been proposed as a reliable indicator of disease prognosis; for example a high ratio of CD8 T cells with a memory phenotype to regulatory T cells has been associated with good therapeutic outcome[15].

Interestingly, it was recently shown that immunity against peritoneal tumors is somewhat unique with regard to mechanisms of protection[16]. The peritoneal cavity harbors resident leukocyte types that are phenotypically and functionally distinct from their counterparts in other anatomic locations. These include B-1b cells[17], peritoneal NK cells[18], and peritoneal macrophages[19]. The functions of these cells in immunity against tumors of the peritoneal cavity is largely unexplored. This exploratory aim is innovative in that we will seek to elucidate changes in the peritoneal tumor immune microenvironment after treatment with different doses of talimogene laherparepvec. This information will facilitate the rational design of combination therapies to target anti- and pro-tumor immune effectors that are relevant to PSD of gastrointestinal, fallopian tube, ovarian, and primary peritoneal cancers.

8.1 Tumor Tissue Biomarkers

Archived formalin fixed paraffin embedded (FFPE) tumor tissue will be collected for all subjects at the end of the study, upon request from the PI (if available). Refer to *Study Manual* for collection, processing, and submission details.

Archived FFPE tumor tissue will be collected and sent to Dr. John Stewart's Laboratory at Louisiana State University (LSU). It will be tested by IHC to evaluate T-cell immune infiltration status, the primary biomarker endpoints for this study. Expression of additional proteins that may be associated with

sensitivity or resistance to the treatment, include but not limited to, CD8, CD3, CD4, PD-L1 and FoxP3. Additionally, NanoString PanCancer Immune profiling RNA panel will be utilized to investigate differential immune gene expression in FFPE samples.

8.2 Immune Cells

Peripheral blood and peritoneal washings will be collected for immune cells from each subject at the following timepoints: baseline (prior to seroconversion dose on C1D1), prior to treatment on C2D1, prior to treatment on C4D1, and 30-day off treatment follow-up. If the subject comes off treatment mid cycle, take an additional plasma sample at the time of disease progression or off treatment. Refer to *Study Manual* for collection and submission details.

Peritoneal immune cells will be processed and stored by the Duke Immune Profiling Core facility under the direction of Dr. Kent Weinhold. Peripheral blood immune cells will be processed and stored by the Substrate Services Core and Research Support (SSCRS) laboratory. All samples will be transferred for analysis to Dr. Stewart's Laboratory at LSU. Polychromatic flow cytometry (PFC) panels will be used to compare treatment related changes in both tumor and peripheral immune cell compartments. Up to 50 markers may be analyzed using 3 PFC panels: 1) a 12-color 'Exhaustion Panel', 2) a 12-color 'Tumor Reactive T Cell Panel', and 3) a 14-color regulatory T cell (Treg) and monocytic myeloid-derived suppressor cells (m-MDSC) panel. This analysis will be overseen by Dr. Stewart.

8.3 Protein Multiplex Arrays (Plasma)

Peripheral blood for plasma will be collected at baseline (prior to seroconversion dose on C1D1), prior to treatment on C1D22, prior to treatment on C2D1, prior to treatment on C3D1, prior to treatment on C4D1, and 30-day off treatment follow up. If the subject comes off treatment mid cycle, take an additional plasma sample at the time of disease progression or off treatment.
Refer to *Study Manual* for collection, processing, and submission details.

Plasma will be stored by the Duke Phase I Biomarker Laboratory under the direction of Dr. Andrew Nixon. Aliquots will be retained from all samples for cytokine analysis by the the Duke Phase 1 Biomarker Laboratory. Remaining plasma samples will be transferred to the Stewart Lab at LSU and markers of inflammation will be analyzed. Analyses will be performed on pre-treatment and on-treatment samples. Analyte levels, and changes in analyte levels, will be correlated with clinical outcome. Plasma and serum samples will be evaluated by ELISA for protein markers that may be associated with sensitivity or resistance to talimogene laherparepvec. These may include, but not limited to, IL1β, IL2, IL4, IL5, IL6, sILR6R, sGP130, IL7, IL8, IL10, IL12, IL13, IL15, IL17A, IL17E, IL22, IL23, IFNγ, TGFβ1, and TGFβ2, but could include other markers that represent best science for this drug and involved signaling pathways.

8.4 Pharmacogenomics (Whole Blood)

Subjects will have whole blood collected at baseline. Refer to *Study Manual* for collection, processing, and submission details.

Whole blood will be stored for possible future analysis of HLA type under the direction of Dr. John Stewart with the consent of the patient.

8.5 Viral Load

Plasma and urine samples will be collected at the following time points: baseline (prior to seroconversion dose on C1D1), C1D8, C1D15, prior to treatment on C1D22, C1D29, prior to treatment on C2D1, prior

to treatment on C3D1, prior to treatment on C4D1, and at 30-day off treatment follow up visit. Peritoneal fluid will be collected at baseline (prior to seroconversion dose on C1D1), prior to treatment on C2D1, prior to treatment on C4D1, and 30-day off treatment follow-up. If the subject comes off treatment mid cycle, take an additional plasma and peritoneal sample at the time of disease progression or off treatment.

Plasma, urine and peritoneal fluid will be will be collected, frozen and stored at the site (at -80) until such time as deemed appropriate for analysis. When ready for viral load analysis, plasma, urine and peritoneal fluid samples will be shipped to Dr. Stewart's lab at LSU. A quantitative primer will be used to detect HSV-1 DNA in plasma, urine, and peritoneal fluid samples via polymerase chain reaction (PCR).

8.6 Peritoneal Cytokine Levels

Peritoneal fluid will be collected at baseline (prior to seroconversion dose on C1D1), prior to treatment on C2D1, prior to treatment on C4D1, and 30-day off treatment follow-up. If the subject comes off treatment mid cycle, take an additional peritoneal fluid sample at the time of disease progression or off treatment.

These samples will be processed and stored by the Duke Immune Profiling Core under the direction of Dr. Kent Weinhold. Supernatent will be transferred to the Duke Phase 1 Biomarker Laboratory under the direction of Dr. Andrew Nixon. Aliquots from all samples will be retained by Dr. Nixon for analysis, including but not limited to, IL1β, IL2, IL4, IL5, IL6, sILR6R, sGP130, IL7, IL8, IL10, IL12, IL13, IL15, IL17A, IL17E, IL22, IL23, IFNγ, TGFβ1, and TGFβ2, but could include other markers that represent best science for this drug and involved signaling pathways. Remaining supernatent will be transferred to Dr. Stewart's lab at LSU for above mentioned viral load analysis via previously described PCR techniques.

8.7 Future Use of Patient Samples

Any remaining biological materials at the end of the study will be deidentified and deidentified samples may be retained for possible use in biomarker research with the consent of the patient. Remaining samples will be retained at the laboratory location of their analysis.

9.0 STATISTICAL ANALYSIS

9.1 General Analysis Considerations

Up to 30 subjects will be enrolled and treated. The intent to treat population is defined as all subjects who receive treatment with talimogene laherparepvec at the MTD.

The per protocol population is defined as all subjects who:

- Undergo treatment with talimogene laherparepvec
- Fulfill all inclusion and exclusion criteria
- Are evaluable for the primary efficacy criterion, TTP

The safety population consists of all the subjects who receive talimogene laherparepvec for whom safety data is available. All safety analyses will be carried out on this population.

9.1.1 Statistical Methods

- The statistical analyses will be performed on the intent to treat, the per protocol, and safety populations.
- Statistical analyses will be only descriptive.
- Descriptive statistics will be provided according to the nature of variables
- Mean, standard deviation, minimum and maximum, median and quartiles will be provided for quantitative variables.
- Percent and frequencies will be provided for qualitative variables.
- Time to events will be illustrated with survival curves using the Kaplan-Meier method.
- Confidence intervals will be constructed from outcomes intent.

9.1.2 Primary Endpoint

The primary objective of the study is to define the safety and toxicity profile of talimogene laherparepvec in patients with peritoneal surface dissemination from gastrointestinal, fallopian tube, ovarian, or primary peritoneal tumors. The MTD across three dose levels will be determined as described in Table 3.1. The safety analyses will be performed on the safety population, as defined above. Incidence of adverse events occurring in 10% or more of patients will be summarized by Grade, overall and by dose level.

Adverse events will be described using the NCI CTCAE 5.0 criteria. Frequency and severity of adverse events according to the NCI CTCAE v 5.0 body system and severity criteria will be described. In addition, frequency of Grade 3 or 4 adverse events will be described separately. Causality will also be noted.

Laboratory assessments will also be described according to the NCI CTCAE criteria, with separate descriptions for Grade 3 or 4 laboratory abnormalities. Clinically significant laboratory abnormalities will be described as well. Serious adverse events will be summarized, including a causality assessment.

9.1.3 Correlative Endpoints

Viral load will be measured by number of copies/mL; patients are expected to have undetectable viral load at baseline and increased viral loads on treatment. Cytokine levels will be measured in pm/mL. For both of these endpoints logarithmic transformations will be used to achieve normality. Immune cell markers will be measured as percentage of subset cell types. Ninety percent (90%) confidence interval (CI) estimates of mean changes in viral load, cytokine levels, and immune markers from baseline will be constructed in the intent-to-treat population (n=12 No preliminary data are available for these endpoints.

The proportion of patients who achieve at least a 2-log change in viral load or cytokine level will be estimated. With 12 patients studied in the intent-to-treat population the 90% upper confidence bound (1-sided) for change in viral load is at most 0.185. The proportion of patients exhibiting at least a 2-log change in cytokine levels (positive or negative) can be estimated to within at most +/- 0.237 with 90% confidence. The proportion of patients exhibiting a change of at least 0.15 in magnitude will be estimated similarly for immune markers.

9.1.4 Exploratory Endpoints

In addition to defining the MTD, the study will provide useful preliminary data concerning efficacy. Methods of assessing response will be specific to each individual patient as described in Section 5.6. In the subset of patients with radiographically measurable disease RECIST 1.1 criteria will be used.

Patients in the per protocol population will be classified as responder or non-responder and the proportion of patients exhibiting response at trial closure by any criteria will be estimated by the 90% confidence interval. Patients who experience a radiographic/tumor marker CR will undergo confirmatory laparoscopy.

Time to progression measured from study entry to documented progression of disease will be estimated by the method of Kaplan-Meier in the intent-to-treat population. Patients who withdraw from the trial prior to disease progression, are either lost to follow-up, die or begin alternative treatments prior to progression, will be censored at the date considered to be lost to follow-up, date of death, or the first day of alternative therapy.

For all efficacy endpoints, analyses will be performed overall and in the patients treated at the MTD. These analyses are primarily exploratory since the data will be from only a limited number of patients available for the study.

As a first approach to addressing our exploratory aim of evaluating changes in peritoneal cavity leukocyte populations after the treatment of peritoneal surface dissemination of gastrointestinal, fallopian tube, ovarian, and primary peritoneal cancers with talimogene laherparepvec, we will perform multi-color flow cytometry analysis on peritoneal lavage fluid from patients at baseline (prior to seroconversion dose on C1D1), prior to treatment on C2D1, and on C4D1. If the subject comes off treatment mid cycle, there will be an additional plasma sample at the time of disease progression or off treatment. Immune cells will be stained with fluorescent antibodies specific for markers of major leukocyte subsets as commonly performed by the Stewart Lab.

9.1.5 Analysis of Baseline Characteristics

The following baseline parameters will be described:

- Age
- Weight
- Hematology
- Serum chemistries
- ECOG performance status
- HSV status

Descriptive statistics for all baseline characteristics will be provided. No tests of significance will be conducted.

9.1.6 Patient Disposition and Agent Exposure

The number of patients treated with intraperitoneal talimogene laherparepvec will be summarized using descriptive statistics. Treatment delays will be summarized using counts and percentages.

Patients' disposition will be summarized in the following manner:

- The number and percentage of patients selected, included, completed, withdrawn and lost to follow-up will be summarized using descriptive statistics
- Major protocol deviations will be summarized.
- The reason for withdrawal (adverse events, lack of efficacy, major protocol deviation, non-medical reason, recovery or remission) will be summarized.

10.0 SAFETY

Refer to *Study Manual* for required reporting forms.

10.1 Adverse Events

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

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

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

AEs may occur during the course of the use of supporting company product(s) in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an AE unless it is considered to be drug related by the Investigator.

AEs will be documented from the date of first dose of study drug through 30 days after the last dose of study drug. All Grade 2-5 AEs as well as special reporting circumstances, such as exposure via a parent during pregnancy or breast-feeding, overdose, medication error, misuse, abuse, off-label use or occupational exposure must be recorded on the CRF.

10.2 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

1. Results in death.
2. Is immediately life-threatening (ie, in the opinion of the Investigator, the AE places the subject at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death).
3. Requires inpatient hospitalization or results in prolongation of an existing hospitalization.
4. Results in persistent or significant disability or incapacity. (Note: The term “disability” refers to events that result in a substantial disruption of a subject’s ability to conduct normal life function.)
5. Is a congenital anomaly or birth defect.

6. Is an important medical event (Note: The term “important medical event” refers to an event that, based upon appropriate medical judgment, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the other serious outcomes listed under the definition of SAE. Examples of important medical events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of product dependency or product abuse.)

SAEs and/or follow up to SAEs including death due to any cause other than progression of the cancer under study, that occurs from the date of the first dose of study drug through 30 days following the last dose of study drug, whether or not related to study drug(s), must be recorded on the CRF and must be reported within 2 working days to Amgen (please see section below for instructions on how to report to Amgen). External sites should report SAEs to the Duke study team within 24 hours. Reporting instructions for external sites can be found in the REDCap study eManual.

All SAEs must be followed until resolution, return to baseline condition, or stabilization. Any SAEs that are ongoing at the time the clinical database is closed will be reported to supporting companies as unresolved.

The initial report for each SAE or death should include at minimum the following information:

- protocol number and title
- patient initials, study identification number, sex, age
- date the event occurred
- description of the event
- seriousness criteria
- event causality or causal relationship
- study drug name(s)
- dose level and cycle number at the time the event occurred
- description of the patient’s condition
- study status of patient at time of report
- responsible investigator name and contact details

The Investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The Investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications. Whenever possible, the Investigator should also provide the batch or lot number of the study drug(s).

SAE Reporting Procedure:

Immediately upon awareness of a SAE, the Investigator (or designee) completes the **DCI SAE Report Form** and will submit the form within 2 business days of knowledge of the event to Amgen. External sites should submit the form within 24 hours to the Duke study team via the REDCap SAE reporting tool. In accordance with applicable regulations, Investigators must report SAEs to their local IRB according to their institutional guidelines.

Note: It is imperative that initial SAE reports are submitted as soon as possible (within 2 business days of knowledge of the event) with available information to the supporting company. Missing and/or clarified event information may be provided in a follow-up report.

Follow-up information including severity, action taken, concomitant medications, and outcome should be communicated to Amgen as soon as possible using the same forms mentioned above.

The Lead PI will review the report form with accompanying source document, sign page 5,and then the PI or designee will promptly submit it to the supporting company.

If the event meets the Duke University Health System (DUHS) IRB reporting requirements, the Duke GI Oncology regulatory coordinator will submit information about the SAE including the Lead PI's assessment as a safety event to the DUHS IRB within 5 business days. Any study-related death must be reported to the IRB within 24 hours of discovery.

Within the time frame outlined in the tables below, the study team will also submit the SAE report form and other relevant safety information to the following supporting company:

Amgen
Fax: 1-888-814-8653
Email: svc-ags-in-us@amgen.com

Safety Reporting to Amgen

The Sponsor/Investigator is responsible for compliance with expedited reporting requirements for serious, unexpected and related adverse events (SUSARs), for generation of SAE reports including narratives, and for periodic reporting to Amgen of SAEs as outlined in the tables below. Documents sent to Amgen should be accompanied by the Cover Page provided in Appendix E. Documents may be faxed to the number provided on the cover page or scanned and sent via email to svc-ags-in-us@amgen.com.

In addition to the requirements outlined in the tables, Sponsor/Investigators are required to report direct exposures to talimogene laherparepvec (e.g., needle stick, splash back) of herpetic illness and all suspected herpetic events.

Table 10.2.1 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 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.

Table 10.2.2 Aggregate Reports

Safety Data	Timeframe for Submission to Amgen
Adverse events (all serious and non-serious adverse events, regardless of relatedness)	Line listing and summary tabulation of **all** adverse events sent annually AND at end of study
US IND Annual Safety Report	Annually
Other Aggregate Analyses (any report containing safety data generated during the course of the study)	At time of ISS sponsor submission to any body governing research conduct (e.g., RA, IRB, etc.)
Final (End of Study) Report, including: • Unblinding data for blinded studies	At time of ISS sponsor submission to any body governing research conduct (e.g., RA, IRB, etc.) but not later than 1 calendar year after study completion

• Reports of unauthorized use of a marketed product	

Expedited Reporting Procedure for Duke Cancer Institute (Coordinating Center):

Duke Cancer Institute as the coordinating center for this study is responsible for reporting SAEs to the FDA in accordance with 21CFR 312.32. Any SAE that is possibly related and unexpected must be submitted to the FDA attached to the IND. If the SAE meets criteria for reporting to the FDA, the study team will complete the Form FDA 3500A (MedWatch) and send to the Lead PI and the supporting companies that are noted above. This submission of the Form FDA 3500A to the FDA attached to the IND will be completed by the Duke GI Oncology Clinical Trials Regulatory Coordinator.

- All unexpected, drug related SAEs that are fatal or life-threatening will be reported to the FDA by phone or fax within 7 calendar days of initial receipt of the information and will provide a complete report within 8 days of the initial report submission (by calendar day 15).

- All unexpected, treatment-related SAEs that are not fatal or life-threatening will be reported in a written report to the FDA within 15 days of initial receipt of the information.

The Duke study team will forward all expedited reports to all participating investigators in the form of an Investigator Alert. The Investigator Alert template is available on the DCI intranet titled “Safety Reporting for Multi-site IITs Notification Email”.

10.3 Events of Clinical Interest

There are no designated events of clinical interest associated with talimogene laherparepvec.

10.3.1 Special Reporting to Amgen

In order to better assess and understand the potential risks to treated patients and/or third parties following the treatment of clinical trial subjects with talimogene laherparepvec, special reporting procedures apply for accidental exposures to talimogene laherparepvec and for suspected herpetic events. See table 10.3.1 for a summary of reporting requirements. Clinicians should review the Imlygic package insert (available online) for additional information on the safe handling of talimogene laherparepvec.

Accidental Exposure of HCPs to Talimogene Laherparepvec

HCPs involved in this trial who are directly exposed to talimogene laherparepvec (e.g., needle stick, splash back) but who are without signs or symptoms of herpetic illness should be reported to Amgen at 1-855-IMLYGIC (1-855-465-9442).

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 HCPs with direct or indirect exposure and (3) suspected herpetic events in treated patients’ close contacts, as outlined in table 10.3.1.

In addition to reporting these events, suspected herpetic lesions should be swabbed and submitted for qPCR 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, however, all lesions should be swabbed, regardless of the timing of presentation. Amgen does not require qPCR or other testing for wild type HSV-1.

- Reporting Process for ISS Treated Patients: Any suspected herpetic lesion should be reported to Amgen at 1-855-IMLYGIC (1-855-465-9442), evaluated by the sponsor/investigator and swabbed for qPCR 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 qPCR testing, which must be obtained prior to swabbing.
- Reporting Process for HCPs and Close Contacts: Sponsor/investigator should advise any HCPs and/or close contacts with suspected herpetic lesions to contact their personal physician to facilitate reporting to Amgen. Suspected herpetic lesions can be reported by the sponsor/investigator, personal physician or exposed individual to Amgen at 1-855-IMLYGIC (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 qPCR testing, which must be obtained prior to swabbing.

Table 10.3.1 Accidental Exposure and Herpetic Event Reporting Requirement Summary

Exposed Person	**Reporter**	**Timeframe for Reporting to Amgen**	**Report Mechanism**	**Timing of Swab Collection**	**qPCR Testing?**	**Responsible Party for Lesion Swabbing**	**qPCR Test Result Distribution**
Treated Patients **with suspected herpetic lesions**	Sponsor / Investigator	Within 24 hours of Sponsor / Investigator awareness	Contact Amgen at 1-855-IMLYGIC (1-855-465-9442) to report event	Collect swabs from suspected lesions (ideally within 3 days of appearance of symptoms)	Yes, if consent obtained	Sponsor / Investigator	Sponsor / Investigator and Amgen
HCP directly exposed to product (e.g., needle stick, splash back) without signs or symptoms of herpetic illness	HCP's Personal Physician or impacted person	Within 24 hours of Reporter awareness	Contact Amgen at 1-855-IMLYGIC (1-855-465-9442) to report event	N/A	N/A	N/A	N/A
HCP directly or indirectly exposed to product **with suspected herpetic lesions**	HCP's Personal Physician or impacted person	Within 24 hours of Reporter awareness	Contact Amgen at 1-855-IMLYGIC (1-855-465-9442) to report event	Collect swabs from suspected lesions (ideally within 3 days of appearance of symptoms)	Yes, if consent obtained	HCP or HCP's Personal Physician	HCP's Personal Physician and Amgen
Close Contact (eg caregiver, spouse, child) **with suspected**	Sponsor / Investigator, Close Contact's Personal Physician or	Within 24 hours of Reporter awareness	Contact Amgen at 1-855-IMLYGIC (1-855-465-9442) to report event	Collect swabs from suspected lesions (ideally within 3 days of	Yes, if consent obtained	Sponsor / Investigator, Close Contact's Personal Physician	Sponsor / Investigator, Close Contact's Personal Physician and Amgen

herpetic lesions	Close Contact			appearance of symptoms)			

*The laboratory conducting the qPCR testing on behalf of Amgen is Viracor.

10.4 Other Safety Considerations

The Investigator must also report in the same timelines as SAEs any incidence of medication error, occupational exposure, abuse or misuse that is associated with or result in an adverse event. All related fatal outcomes must also be reported in the same timeline as a SAE.

Refer to SAE reporting procedures in Section 10.2.

10.4.1 Pregnancy and Lactation

Although pregnancy and lactation are not considered adverse events, it is the responsibility of Investigator or designee to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 90 days of following cessation of treatment. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (important medical events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported in the same procedure as an SAE. Refer to SAE reporting procedures in Section 10.2. Pregnancy and lactation must also be reported to Amgen, using Amgen provided forms. See Amgen reporting information above.

Adequate and well-controlled studies with talimogene laherparepvec have not been conducted in pregnant women. No effects on embryo-fetal development have been observed in animal studies. If talimogene laherparepvec is used during pregnancy, or if the subject becomes pregnant while taking talimogene laherparepvec, the subject should be apprised of the potential hazards to the fetus and/or neonate. Women of childbearing potential should be advised to use an effective method of contraception to prevent pregnancy during treatment with talimogene laherparepvec.

If a pregnant woman has an infection with wild-type HSV-1 (primary or reactivation), there is potential for the virus to cross the placental barrier and also a risk of transmission during birth due to viral shedding. Infections with wild-type HSV-1 have been associated with serious adverse effects, including multi-organ failure and death, if a fetus or neonate contracts the wild-type herpes infection. While there are no clinical data to date on talimogene laherparepvec infections in pregnant women, there could be a risk to the fetus or neonate if talimogene laherparepvec were to act in the same manner. No effects on embryo-fetal development were observed when talimogene laherparepvec was administered during organogenesis to pregnant mice at doses up to 4×10^8 (400 million) PFU/kg (60-fold higher, on a PFU/kg basis, compared to the maximum clinical dose). Negligible amounts (< 0.001% of maternal blood levels) of talimogene laherparepvec DNA were found in fetal blood.

Females:
No studies of the effects of talimogene laherparepvec on reproduction and development have been performed. Women who can become pregnant must use acceptable methods of contraception. If a woman becomes pregnant or suspects she is pregnant during the study, she should inform the Principal

Investigator or study staff immediately. The Principal Investigator should notify Amgen of the pregnancy (via the Pregnancy Notification Worksheet) and discuss follow-up with the subject.

Males:
Male subjects should be advised to inform the Principal Investigator or study staff immediately in the event that their female partner becomes pregnant during the study or if she was pregnant at the time of study enrollment. Upon receipt of this information, the Principal Investigator should notify Amgen Global Patient Safety of the pregnancy (via the Pregnancy Notification Worksheet), and discuss follow-up regarding the pregnancy outcome with the subject.

No studies of talimogene laherparepvec have been conducted in breastfeeding women. Talimogene laherparepvec should not be used during breastfeeding. Breastfeeding women and women planning on breastfeeding may not participate in clinical trials with talimogene laherparepvec. If a woman breastfeeds during the study, she must tell her Principal Investigator or study staff immediately. The Principal Investigator should notify Amgen (via the Lactation Notification Worksheet) that the subject has breastfed the infant and discuss follow-up with the subject.

10.4.2 Medication Overdose

If an adverse event(s) is associated with ("results from") the overdose of study drug(s), the adverse event(s) is reported as a SAE, even if no other seriousness criteria are met. Refer to SAE reporting procedures in Section 10.2.

There is no clinical experience with overdosage of talimogene laherparepvec. Doses up to 4 mL at a concentration of 10^8 PFU/mL every 2 weeks have been administered in clinical trials with no evidence of dose limiting toxicity. The maximum dose of talimogene laherparepvec that can be safely administered has not been determined. In the event of a suspected overdose, the patient should be treated symptomatically and supportive measures instituted as required.

10.5 Safety Review for Dose Escalation

During the Dose Escalation phase, patients will be enrolled according to a standard '3+3' design. Each subject will have weekly study visits with safety assessments for the first 5 weeks on treatment (cycle 1). Once the first dose level has completed enrollment and completed cycle one, enrollment will be placed on hold and a safety review will be conducted. The PI, co-PI, and study chair will meet and review the safety data for DLTs up to that point. Based on their review, the group will determine whether study enrollment can proceed at the next dose level or the MTD has been reached based on the rules outlined in section 3.2. The PI or designee will inform the funding company of the outcome of the safety review.

11.0 ADMINISTRATIVE RESPONSIBILITIES

11.1 Institutional Review Board/Independent Ethics Committee

Before study initiation, the Investigator must have written and dated approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects.

The Investigator should provide the IRB/IEC with reports, updates, and other information (e.g., Safety Updates, Amendment IRB/IECs, and Administrative Letters) according to regulatory requirements and institution procedures.

Copies of all IRB/IEC approvals, as well as annual re-approvals and approved/stamped informed consent forms must be submitted to Duke GI Oncology Clinical Trials Office.

11.2 Protocol and Protocol Revisions

All revisions to the protocol must be reviewed and approved by Amgen prior to IRB submission. Once approved by Amgen and the Duke IRB, revised protocol versions will be provided to Amgen by the Lead PI or designee(s) at the Duke GI Oncology Clinical Trials Office. The Lead PI must have written and dated approval/favorable opinion from the Duke University Health System (DUHS) IRB of revised protocol prior to distribution to Investigators at external participating sites.

Investigators must obtain written and dated and approval/favorable opinion from the IRB/IEC before conducting any updated protocol version. Study must be conducted as described in the approved protocol. The Investigator must not implement changes of the approved protocol without prior written agreement by the Lead PI and prior review and documented approval/favorable agreement by the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the changes involve only logistical or administrative aspects of the study (e.g., changes in research personnel or change in phone numbers).

Documentation of approval(s) from the IRB/IEC must be sent to Duke GI Oncology Clinical Trials Office.

11.3 Protocol Deviations and Violations

A protocol deviation is non-adherence to protocol specific study procedures or schedules that does not involve inclusion/exclusion criteria, primary objective evaluation criteria, and/or Good Clinical Practice (GCP) guidelines.

A protocol violation is any significant divergence from the protocol such as non-adherence on the part of the subject, the Investigator, or the sponsor to protocol specific inclusion/exclusion criteria, primary objective evaluation criteria, and/or GCP guidelines.

As a matter of policy, the Lead PI (ie. sponsor) will not grant exceptions to protocol specific entry criteria to allow subjects to enter a study. If it is found that a subject who did not meet protocol eligibility criteria was entered in a study (a protocol violation), the Lead PI and/or designee(s) at the Duke GI Oncology Clinical Trials Office must be informed immediately. Such subjects will be discontinued from the study, except in an exceptional instance following review and written approval by the Lead PI and the responsible IRB/IEC.

Protocol deviations and violations must be documented and reported to the Lead PI and/or designee(s) at the Duke GI Oncology Clinical Trials Office.

In accordance with applicable regulations, Investigators must report protocol deviations and violations to their local IRB/IEC according to their institutional guidelines.

11.4 Informed Consent

The Investigator must ensure that subjects or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which

they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and their IRB. A copy of the proposed informed consent document must be submitted to the Lead PI or designee(s) at the Duke GI Oncology Clinical Trials Office for review and comment prior to submission to the local IRB/IEC.

Informed consent must be obtained prior to performing any study-related procedures that are not part of normal subject care, including screening and changes in medications. A copy of the signed informed consent form must be given to the study subject.

11.5 Source and Study Documentation

Source documents include all original recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. Accordingly, source documents include, but are not limited to, laboratory reports (including normal and abnormal results), radiology reports, subject diaries, biopsy reports, ultrasound photographs, subject progress notes, hospital charts or pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original certified document.

When clinical observations are entered directly into an electronic medical record system (i.e. in lieu of original hardcopy records), the electronic record can serve as the source document if the system has must be validated to meet the FDA requirements for electronic records and signatures (i.e. meets 21 CFR Part 11 compliant).

Regulations require that Investigators maintain information in the study subject's medical records which corroborate data recorded on the CRF. In order to comply with these regulatory requirements, the following information will be maintained and made available as required by the Lead PI or designee(s), monitors, and/or regulatory inspectors:

- Medical history/physical condition of the study subject prior to involvement in the study sufficient to verify protocol entry criteria.
- Dated note that informed consent was obtained for the subject's participation in the study.
- Dated and signed notes for each subject visit including results of examinations.
- Notations on abnormal lab results and their resolution.
- Dated reports of special assessments (e.g., ECG reports).
- Dated and signed notes regarding adverse events (including event description, severity, onset date, duration, relation to study treatment, outcome and treatment for adverse event).
- Dated notes regarding concomitant medications taken during the study (including start and stop dates).
- Subject condition upon completion of or withdrawal from the study.

Study documentation includes all CRFs, data correction forms, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence and regulatory documents (e.g., protocol and amendments, IRB/IEC correspondence and approvals, approved and signed subject consent forms, Statement of Investigator form, and clinical study supplies receipts and distribution records).

The Investigator will prepare and maintain complete and accurate study documentation in compliance with GCP guidelines and applicable federal, state, and local laws, rules and regulations; and, for each

subject participating in the study, promptly complete all CRFs and such other reports as required by this protocol following completion or termination of the clinical study or as otherwise required pursuant to any agreement with the Lead PI and Duke Cancer Institute (DCI).

The Investigator acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, study documentation will be promptly and fully disclosed to Lead PI or designee(s) by the Investigator upon request and also shall be made available at the Investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Lead PI and DCI or responsible government agencies as required by law.

The Investigator agrees to promptly take any reasonable steps that are requested by the Lead PI or designee(s) as a result of an audit to cure deficiencies in the study documentation and case report forms.

11.6 Case Report Forms

Subject data will be entered (ie. CRFs completed) into an electronic data capture (EDC) system called Medidata RAVE. This database is maintained on a secure Duke University server and is accessible via internet with login and password.

CRFs should be completed by trained study personnel according to guidelines provided by the Lead PI or designee(s) at the Duke GI Oncology Clinical Trials Office. The Investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. The Investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the Investigator confirms that all recorded data have been verified as accurate.

In the event of discrepant data, the study monitor or study designee will request data clarification from the Investigator or designee for which may be resolved electronically in the EDC system.

Accurate and reliable data collection will be ensured through verification and crosscheck of the CRFs against the Investigator's study records (source document verification) by the study monitor or study designee.

11.7 Monitoring and Audits/Inspections

The study will be monitored both internally by the Lead PI and externally by the Duke Cancer Institute (DCI) Monitoring Team in accordance with their NCI-approved "Institutional Protocol Monitoring Procedures and Guidelines for NIH-sponsored Research Involving Human Subjects".

In terms of internal review, the Lead PI and/or designee(s) will continuously monitor and tabulate adverse events. Appropriate reporting to the DUHS IRB will be made. If an unexpected frequency of Grade 3 or 4 adverse events occurs, depending on their nature, action appropriate to the nature and frequency of these adverse events will be taken. This may require a protocol amendment, dose de-escalation, or potentially closure of the study. The Lead PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled (if applicable);
- Stopping rules for toxicity and/or response are met;
- Risk/benefit ratio is not altered to the detriment of the subjects;

- Appropriate internal monitoring of adverse events and outcomes is done;
- Over-accrual does not occur;
- Under-accrual is addressed with appropriate amendments or actions;
- Data are being appropriately recorded on the CRF in a reasonably timely manner.

The Duke Cancer Institute (DCI) Monitoring Team will conduct monitoring visits to ensure subject safety and to ensure that the protocol is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, GCP, and applicable regulatory requirements. As specified in the DCI Data and Safety Monitoring Plan, the DCI Monitoring Team will conduct routine monitoring after the third subject is enrolled, followed by annual monitoring of 1-3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk.

An external site monitoring plan addendum describes monitoring at participating sites.

Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns and may be initiated upon request of DUHS and DCI leadership, the DCI Cancer Protocol Committee, the Safety Oversight Committee (SOC), the sponsor, the Principal Investigator, or the IRB. All study documents must be made available upon request to the DCI Monitoring Team and other authorized regulatory authorities, including but not limited to the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

The DCI Safety Oversight Committee (SOC) will perform annual reviews on findings from the DCI Monitoring Team visit and additional safety and toxicity data submitted by the Principal Investigator.

DCI Quality Assurance personnel, or designee, may conduct audits at sites. Audits will include, but not be limited to: audit trail of data handling and processes, SOPs, drug supply, presence of required documents, the informed consent process, and comparison of case report forms/database with source documents. The Investigator agrees to accommodate and participate in audits conducted at a reasonable time in a reasonable manner, as needed.

Regulatory authorities may also audit an Investigator during or after the study. The Investigator should contact the Lead PI and designee(s) at the Duke GI Oncology Clinical Trials Office as well as their local IRB, immediately if this occurs, and must fully cooperate with governmental (e.g., FDA) audits conducted at a reasonable time in a reasonable manner.

The Duke University Compliance Program - Human Subject Research Compliance (HSRC) section may conduct confidential audits to evaluate compliance with the protocol and the principles of GCP. The Lead PI agrees to allow the HSRC auditor(s) direct access to all relevant documents and to allocate his/her time and the time of the study team at the Duke GI Oncology Clinical Trials Office to the CTQA auditor(s) in order to discuss findings and any relevant issues.

11.8 Study Closeout

Upon completion of the study (defined as all subjects have completed all follow-up visits, all CRFs are complete, and all queries have been resolved) the Lead PI or designee(s) at the Duke GI Oncology Clinical Trials Office will notify the Investigator of closeout and a study closeout visit will be performed.

The study monitor or study designee will ensure that the Investigator's regulatory files are up to date and complete, and that any outstanding issues from previous visits have been resolved. Other issues to be reviewed at the closeout visit include: retention of study files, possibility of site audits, publication

policy, and study closure with local IRB. The final study report must be submitted to Amgen prior to study closeout.

11.9 Records Retention

The Investigator will maintain the records of study drug disposition, worksheets and all other study-specific documentation (e.g., study files, source documentation) until notified by the Lead PI or designee(s) at the Duke GI Oncology Clinical Trials Office that records may be destroyed. If the application is not filed or is withdrawn, the Investigator will maintain the records for at least two (2) years after the formal discontinuation of the clinical development program for this product(s).

To avoid error, the Investigator will contact the Lead PI or designee(s) at the Duke GI Oncology Clinical Trials Office before the destruction of any records pertaining to the study to ensure they no longer need to be retained. In addition, the Lead PI or designee(s) will be contacted if the Investigator plans to leave the institution so that arrangements can be made for the transfer of records.

12.0 REFERENCES

1. Teo, M., *Peritoneal-based malignancies and their treatment.* Ann Acad Med Singapore, 2010. **39**(1): p. 54-7.
2. Chang, G.J. and L.A. Lambert, *Hidden opportunities in cytoreductive surgery for peritoneal carcinomatosis of colorectal origin.* Ann Surg Oncol, 2008. **15**(11): p. 2993-5.
3. Al-Shammaa, H.A., Y. Li, and Y. Yonemura, *Current status and future strategies of cytoreductive surgery plus intraperitoneal hyperthermic chemotherapy for peritoneal carcinomatosis.* World J Gastroenterol, 2008. **14**(8): p. 1159-66.
4. McCusker, M.E., et al., *Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973-1998.* Cancer, 2002. **94**(12): p. 3307-12.
5. Hasovits, C. and S. Clarke, *Pharmacokinetics and pharmacodynamics of intraperitoneal cancer chemotherapeutics.* Clin Pharmacokinet, 2012. **51**(4): p. 203-24.
6. Elsedawy, N.B. and S.J. Russell, *Oncolytic vaccines.* Expert Rev Vaccines, 2013. **12**(10): p. 1155-72.
7. Senzer, N.N., et al., *Phase II clinical trial of a granulocyte-macrophage colony-stimulating factor-encoding, second-generation oncolytic herpesvirus in patients with unresectable metastatic melanoma.* J Clin Oncol, 2009. **27**(34): p. 5763-71.
8. Agarwala, S.S., *The Role of Intralesional Therapies in Melanoma.* Oncology (Williston Park), 2016. **30**(5): p. 436-41.
9. Andtbacka, R.H., et al., *Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma.* J Clin Oncol, 2015. **33**(25): p. 2780-8.
10. Puzanov, I., et al., *Talimogene Laherparepvec in Combination With Ipilimumab in Previously Untreated, Unresectable Stage IIIB-IV Melanoma.* J Clin Oncol, 2016. **34**(22): p. 2619-26.
11. Dineen, S.P., et al., *A Simplified Preoperative Assessment Predicts Complete Cytoreduction and Outcomes in Patients with Low-Grade Mucinous Adenocarcinoma of the Appendix.* Ann Surg Oncol, 2015. **22**(11): p. 3640-6.
12. Mazzei, M.A., et al., *Accuracy of MDCT in the preoperative definition of Peritoneal Cancer Index (PCI) in patients with advanced ovarian cancer who underwent peritonectomy and hyperthermic intraperitoneal chemotherapy (HIPEC).* Abdom Imaging, 2013. **38**(6): p. 1422-30.
13. Wang, D., et al., *Antitumor activity and immune response induction of a dual agonist of Toll-like receptors 7 and 8.* Mol Cancer Ther, 2010. **9**(6): p. 1788-97.
14. Lizotte, P.H., et al., *Attenuated Listeria monocytogenes reprograms M2-polarized tumor-associated macrophages in ovarian cancer leading to iNOS-mediated tumor cell lysis.* Oncoimmunology, 2014. **3**: p. e28926.
15. Pages, F., et al., *Immune infiltration in human tumors: a prognostic factor that should not be ignored.* Oncogene, 2010. **29**(8): p. 1093-102.
16. Sedlacek, A.L., et al., *Generation of a dual-functioning antitumor immune response in the peritoneal cavity.* Am J Pathol, 2013. **183**(4): p. 1318-28.
17. Berland, R. and H.H. Wortis, *Origins and functions of B-1 cells with notes on the role of CD5.* Annu Rev Immunol, 2002. **20**: p. 253-300.
18. Gonzaga, R., P. Matzinger, and A. Perez-Diez, *Resident peritoneal NK cells.* J Immunol, 2011. **187**(12): p. 6235-42.
19. Liu, G., et al., *The macrophage heterogeneity: difference between mouse peritoneal exudate and splenic F4/80+ macrophages.* J Cell Physiol, 2006. **209**(2): p. 341-52.
20. Talimogene Laherparepvec [Investigator's Brochure]. Amgen Inc., Thousand Oaks, CA; 23 January 2016.
21. Sasenk, M., O. Fillipova, and W.P. Tes, *Fallopian tube carcinoma*. J Oncol Pract, 2019. **15**(7): p. 375-382.

22. Bergsten, T.M., F.E. Burdette, M. Dean, *Fallopian tube initiation of high grade serous ovarian cancer and ovarian metastasis: Mechanicsms and therapeutic implications*. Cancer Lett, 2020. 476: p. 152-160.

Appendix A. RECIST 1.1

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

Definitions
Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (version 1.1). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease
Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10mm)
- 10mm caliper measurement by clinical exam (when superficial)
- 20mm by chest X-ray (if clearly defined and surrounded by aerated lung)

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease
All other lesions (or sites of disease), including small lesions (longest diameter ≥10 to <15 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

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

Cystic lesions:

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

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions
All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm x 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and >10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

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

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

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

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors,

where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Response Criteria

Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-target Lesions
While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concept apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New Lesions
The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline

lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow- up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response
The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response."

The best overall response is determined once all the data for the patient is known. Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Appendix B. ECOG Performance Status

The ECOG Scale of Performance Status, developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair*, describes a patient's level of functioning in terms of their ability to care for themself, daily activity, and physical ability (walking, working, etc.).

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

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

Appendix C. Study Calendar

Study Procedures	Screening Period	Peritoneal Catheter Placement	Treatment Period[1]					Follow-up Period[2]		
	Days -28 to -5 (+/-2 days)	(Day -6 to -2)	Cycle 1			Cycles 2 to 4 Day 1[21]	At 12 weeks (C4 D14)[21]	30 (±7) Days	Long Term F/U	Survival F/U
			D1	D8, 15, 29	D22					
Informed Consent	X[3]									
Demographics	X									
Medical and Cancer History	X									
Concomitant Medications	X		X[4]							
Physical Examination	X		X	X	X	X		X		
Abdominal Measurement[20]	X		X			X		X		
Height	X									
Vital Signs and Weight[5]	X		X[19]	X	X[19]	X[19]		X		
ECOG Performance Status	X		X	X	X	X		X		
CBC with Differential[8]	X[6]		X[6]	X	X	X		X		
Chemistries including LFTs[8]	X[6]		X[6]	X	X	X		X		
Coagulation Tests	X									
Serum Pregnancy Test[7]	X[16]							X		
TVEC Administration[9]			X		X	X				
Place Peritoneal Catheter[23]		X								
Remove Peritoneal Catheter								X[22]		
Adverse Event Assessment	X		X[4]							
Tumor Assessment[10]	X[25]						X[25]		X[17,25]	
Blood Tumor Markers[18]	X						X		X[17]	
Archived Tumor Tissue[11]									X	
Viral Load[12]			X[12]	X[12]	X[12]	X[12]		X		
Peritoneal Cytokines[13]			X[13]			X[13]		X[13]		
Immune Cells[14]			X[14]			X[14]		X[14]		

Study Procedures	Screening Period	Peritoneal Catheter Placement	Treatment Period[1]					Follow-up Period[2]		
	Days -28 to -5 (+/-2 days)	(Day -6 to -2)	Cycle 1			Cycles 2 to 4 Day 1[21]	At 12 weeks (C4 D14)[21]	30 (±7) Days	Long Term F/U	Survival F/U
			D1	D8, 15, 29	D22					
Plasma[15]			X[15]		X[15]	X[15]		X[15]		
Whole Blood (for pharmacogenomics)[16]	X									
Survival									X[24]	X[24]

1. Cycle length is 2 weeks, with the exception of Cycle 1, which is 5 weeks long.
2. Follow up visit to be completed for all subjects at 30 days after last dose of study drug. For subjects that complete or discontinue treatment without documented disease progression, subjects will have Long Term follow-up every 12 weeks or as clinically indicated until documented disease progression or subsequent anti-cancer treatment. All patients will have Survival Follow-up for up to 1 year after completing study treatment.
3. May be completed more than 28 days prior to Cycle 1 Day 1.
4. Document this data throughout the study when changes or events occur.
5. Obtain temperature (°C), blood pressure, heart rate and weight (kg).
6. Must perform within 3-7 days prior to Cycle 1 Day 1 for patients with peritoneal port placed on study. Must be performed within 7 days prior to Cycle 1 Day 1 for patients with pre-existing peritoneal port. If completed within 7 days of Cycle 1 Day 1, no need to repeat.
7. Only for women of childbearing potential
8. After Cycle 1, may perform up to 3 days prior to Day 1.
9. Seroconversion dose of $4x10^6$ PFU on Cycle 1 Day 1. Three weeks after initial seroconversion dose, talimogene laherparepvec administered at dose level every 2 weeks for up to 4 doses.
10. Radiographic assessments (i.e. restaging scans) include CT and/or MRI of chest, abdomen and pelvis after at least 8 weeks on study treatment. Same method for tumor assessment should be employed at every assessment.
11. Archived tumor will be collected at the end of the study, upon request from the PI, if FFPE tumor tissue is available. Refer to [Section] and Study Manual.
12. At baseline (prior to seroconversion dose on C1D1), C1D8, C1D15, prior to treatment on C1D22, C1D29, prior to treatment on C2D1, prior to treatment on C3D1, prior to treatment on C4D1, and 30-day off treatment follow up. If the subject comes off treatment mid cycle, take an additional plasma, urine, and peritoneal fluid samples at the time of disease progression or off treatment. *Note: C1D8, C1D15, C1D22, C1D29 and C3D1 timepoints are only for plasma and urine.
13. Peritoneal fluid for cytokines will be collected at baseline (prior to seroconversion dose on C1D1), prior to treatment on C2D1, prior to treatment on C4D1, and 30-day off treatment follow-up. If the subject comes off treatment mid cycle, take an additional peritoneal fluid sample at the time of disease progression or off treatment.
14. Peripheral blood and peritoneal washings collected at baseline (prior to seroconversion dose on C1D1), prior to treatment on C2D1, prior to treatment on C4D1, and 30-day off treatment follow-up. If the subject comes off treatment mid cycle, take an additional blood and peritoneal wash sample at the time of disease progression or off treatment.
15. At baseline (prior to seroconversion dose on C1D1), prior to treatment on C1D22 prior to treatment on C2D1, prior to treatment on C3D1, prior to treatment on C4D1, and 30-day off treatment follow-up. If the subject comes off treatment mid cycle, take an additional plasma sample at the time of disease progression or off treatment.
16. Whole blood collected at baseline only. May be obtained on C1D1 prior to treatment.
17. Subjects are followed every 12 weeks or as indicated until disease progression or start of new anti-cancer therapy.
18. CEA for appendiceal cancer, CA-125 for ovarian cancer, or other tumor markers as appropriate for disease.
19. On days when drug is administered, take vitals every 15 minutes for the first hour after infusion, then observe for 1 hour and redo vitals at end of 2-hour observation.
20. Measurement of abdominal girth
21. A window of +/- 3 days is allowed for day 1 visits for each cycle, as well as the restaging visit.
22. The treating physician can leave the catheter if they anticipate using for other IP therapies. If catheter is removed, treating physician may also determine whether it is clinically indicated to do PT/PTT.
23. Peritoneal catheter must be placed after eligibility confirmation.
24. Survival follow up every 3 months. May be completed by phone or in person interview, or medical record review.
25. Radiographic assessments should be evaluated by RECIST 1.1.

Appendix D. Laboratory Tests

CBC with differential		
• hematocrit • hemoglobin • platelet count	• WBC (total and differential) • red blood cell (RBC) count	• absolute neutrophil count • absolute lymphocyte count
Chemistries with liver function tests (LFTs)		
• albumin • alkaline phosphatase (ALP) • ALT • AST • bicarbonate	• blood urea nitrogen (BUN) • chloride • creatinine • glucose • calcium	• potassium • sodium • total bilirubin • total protein
Pregnancy Test		
• serum β-HCG pregnancy test		