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NCI Protocol #: 10058

Local Protocol #: *NCI10058*

ClinicalTrials.gov Identifier: NCT03300544

TITLE: A PHASE I STUDY OF TALIMOGENE LAHERPAREPVEC (TALIMOGENE LAHERPAREPVEC) WITH NEOADJUVANT CHEMOTHERAPY AND RADIATION IN ADENOCARCINOMA OF THE RECTUM

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NCI-Supplied Agent(s): Talimogene laherparepvec, NSC 785349
Other Agent(s): 5-fluorouracil, capecitabine, oxaliplatin, external beam radiation (supplier for all agents, commercial)

IND: *TBD*

IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date:

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Revision 6/version date 06/27/2017
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**Protocol types: Original, Revision, or Amendment*

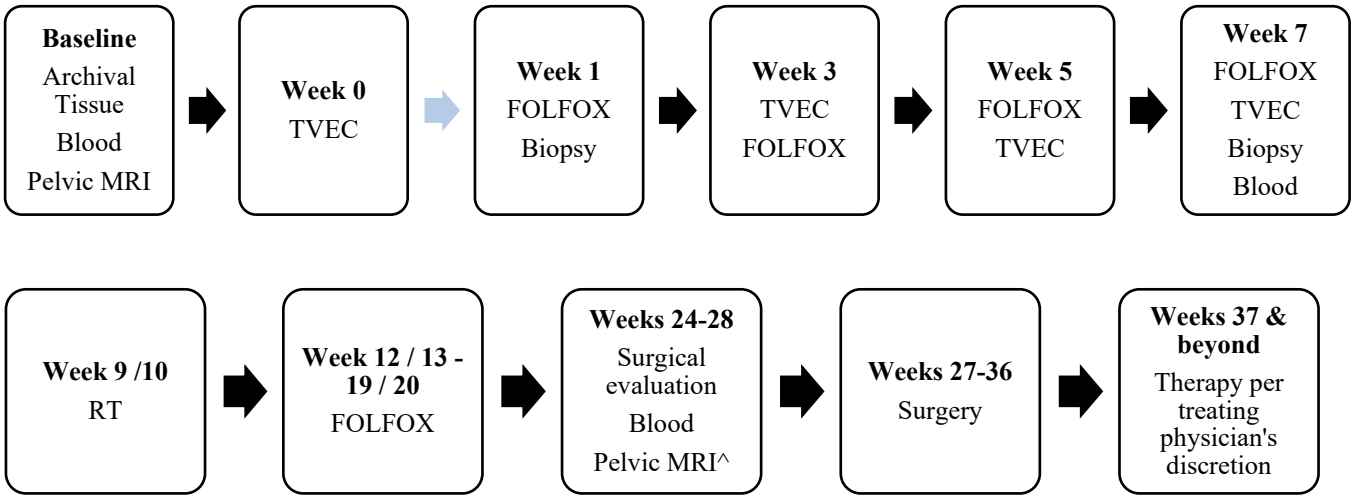
SCHEMA

- Patients with rectal adenocarcinoma either locally advanced or metastatic rectal adenocarcinoma requiring chemoradiation to the primary lesion are eligible.
- Patients with locally advanced rectal adenocarcinoma (T3 or T4, at risk of having a positive surgical radial margin and/or N+), or patients with metastatic disease requiring chemoradiation.
- Patients will be treated with FOLFOX chemotherapy x 4 doses over 8 weeks (weeks 1-8) followed by short course radiation over 5 days (weeks 9 or 10).
- Subsequently, starting approximately 2 weeks after finishing short course RT, patients will receive FOLFOX chemotherapy x 4 doses (weeks 12 / 13 – 19 / 20). While surgical resection of the primary is not mandatory, those requiring surgery will undergo resection 8-16 weeks later (weeks 27 - 36) and / or further systemic therapy per treating physician's discretion.
- Talimogene laherparepvec will be administered via endoscopy by a qualified physician for a total of 4 doses at the following time points: a) week prior to c1 FOLFOX b) weeks 3, 5 and 7 during FOLFOX
- Dose escalation will be done using a 3 + 3 design over 2 cohorts and a total of 15 patients

Dose level+	**TALIMOGENE LAHERPAREPVEC Dose (PFU/ml)**	**Capecitabine (mg/m^2 po bid on days of radiation)**	**Radiation**	**Comments**
1	1x 10^6, 1x 10^7, 1x 10^7,1x 10^7	825	50.4 Gray in 28 fractions	Completed prior to protocol amendment 1/23/21
1 (amended)	1x 10^6, 1x 10^7, 1x 10^7,1x 10^7	N/A	25 Gray in 5 fractions	To be implemented if DLTs noted with DL 2
2	1x 10^6, 1x 10^8, 1x 10^8, 1x 10^8	N/A	25 Gray in 5 fractions	

will be treated at MTD.

Dose limiting toxicities (DLTs) will be captured until completion of FOLFOX chemotherapy (weeks 18/9) and will be graded according to the CTCAE ver 5.0.



#Patients with inadequate archival tissue for integrated biomarker analysis
^As part of pre-surgical evaluation or at a corresponding time point in patients not undergoing surgery
+Dose escalation will be done using a 3+3 design for a total of 15 patients that will be treated at MTD
TVEC = talimogene laherparepvec

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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To determine the dose limiting toxicities (DLTs) and maximum tolerated dose (MTD) of talimogene laherparepvec in combination with chemotherapy and radiation in rectal cancer

1.2 Secondary Objectives

1.2.1 To establish safety and feasibility of the combination
1.2.2 To determine the neoadjuvant rectal (NAR) score of talimogene laherparepvec with chemotherapy and radiation

Although the clinical benefit of this combination of drugs has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.

1.3 Exploratory Objectives

1.3.1 To correlate genomic information including RAS, RAF mutation status with response, DFS and / or OS.
1.3.2 To determine immunodulatory changes following talimogene laherparepvec, chemotherapy and radiation treatment including proportions of immune cell infiltrates in serially collected peripheral blood and/or frozen tumor samples (pre-, on treatment, and at post progression)
1.3.3 To identify MRI-based features including mrCRM at baseline or post-therapy mrCRM, mrTRG to define determinants of response, DFS and OS
1.3.4 To determine the disease free survival (DFS) and overall survival (OS) of talimogene laherparepvec with chemotherapy and radiation in patients undergoing curative resection
1.3.5 To determine the pathological complete response (pCR) rate of talimogene laherparepvec with chemotherapy and radiation

2. BACKGROUND

2.1 Rectal Adenocarcinoma

In the United States, approximately 40,000 new cases of rectal cancer are diagnosed annually[1]. The current standard of care for neoadjuvant rectal cancer in North America includes preoperative long course concurrent chemoradiation followed by surgery with total mesorectal excision (TME),

which is then followed by adjuvant systemic chemotherapy.

The role of preoperative chemoradiation is based on the pivotal phase III German Rectal Cancer trial (CAO/ARO/AIO-94) that demonstrated that neoadjuvant fluoropyrimidine-based chemoradiation followed by TME was an effective strategy to reduce rates of local recurrence and adherence with completion of therapy. Preoperative therapy when compared to post-operative therapy led to significant down staging of tumor burden (25% vs 40% with positive lymph nodes, $p < 0.001$), a larger number of patients were able to avoid abdominoperineal resection requiring permanent colostomy (39% vs 19%; $p = 0.004$), lower rates of grade 3-4 acute and chronic side effects (27% vs 40%, $p = 0.001$; 14% vs 24%, $p = 0.01$ respectively), and lower rate of local recurrence (7.1% vs 10%, $p = 0.048$) at 10 year follow up[2, 3]. More recently, several phase III trials have compared 5-FU to its oral pro-drug, capecitabine in the neoadjuvant setting noting equivalency in pathologic complete response (NSABP R-04, MARGIT)[4]. Due to the optimization of local tumor control with improved preoperative diagnostic imaging, preoperative radiotherapy and TME, local recurrence rates have dropped to 5-10%. Disappointingly, these advances in local control have not translated into an overall survival benefit. Distant relapse rates continue to be high at 30-35% approaching 50% in certain high-risk cases ($T3\text{-}_4$, $N_{2\text{-}3}$, and / or positive radial margin). Furthermore, significant risk of morbidity remains with rectal surgery including the need for a temporary or permanent colostomy, anorectal sphincter dysfunction, urinary and sexual dysfunction.

Well-established data show that degree of response to neoadjuvant therapy correlate with long term survival in patients with rectal cancer. For instance, a large retrospective study by our group suggest that patients with pathological complete response (pCR) to neoadjuvant chemoradiation have significantly low risk of distant metastatic recurrence (7% vs10.1% vs 26.5%, $p < 0.001$) and significantly better relapse free survival (RFS; 90.5% vs 78.7% vs 58.5%, $p < 0.001$) compared to those with intermediate or poor response. Furthermore, patients with pCR are increasingly being managed with conservative management without surgery[5]. However, with the current approach, only 15-20% of all patients have pCR. Therefore, making neoadjuvant therapy for rectal cancer more effective to improve pCR, and ultimately overall survival (OS) is an urgent, unmet need. The traditional approach of testing agents active in the metastatic setting as radiosensitizers has largely been abandoned given the multiple negative trials that did not demonstrate an improvement in pCR but resulted in increased toxicities. Novel radiosensitizers that improve response to neoadjuvant therapy in rectal cancer are thus needed urgently.

The protocol was amended after completion of the first cohort of dose escalation to replace chemoradiation with short course radiation based on emerging data from ASCO 2020 and shifting practice patterns post COVID. The RAPIDO trial was an investigator-driven, open-label, randomized, controlled, phase 3 trial in patients with locally advanced rectal cancer classified as high risk based on pelvic MRI (with at least one of the following criteria: clinical tumor [cT] stage cT4a or cT4b, extramural vascular invasion, clinical nodal [cN] stage cN2, involved mesorectal fascia, or enlarged lateral lymph nodes). Patients allocated to the experimental treatment group received short-course radiotherapy (5×5 Gy) followed by chemotherapy with fluoropyrimidine and oxaliplatin for up to 18 weeks followed by total mesorectal excision. Patients allocated to the standard of care group received long course chemoradiation up to 50·4 Gy concomitant twice-

daily oral capecitabine 825 mg/m^2 followed by total mesorectal excision and, if stipulated by hospital policy, adjuvant chemotherapy with CAPOX or f FOLFOX4. Median follow-up was 4·6 years. At 3 years after randomization, the cumulative probability of disease-related treatment failure, the primary endpoint was 23·7% (95% CI 19·8–27·6) in the experimental group versus 30·4% (26·1–34·6) in the standard of care group (hazard ratio 0·75, 95% CI 0·60–0·95; p=0·019). Serious adverse events occurred in 177 (38%) of 460 participants in the experimental group and, in the standard of care group, in 87 (34%) of 254 patients without adjuvant chemotherapy and in 64 (34%) of 187 with adjuvant chemotherapy.

This trial thus established the efficacy and safety of short course radiation.
During the COVID pandemic, with an intent towards reducing patient time in health care settings, short course radiation has been recommended by multiple consensus guidelines, was rapidly implemented across the country and is now standard of care for locally advanced rectal cancer patients. The protocol will be amended to replace chemoradiation with short course radiation for dose level 2 as below.

2.2 CTEP IND Agents

2.2.1 Talimogene laherparepvec (talimogene laherparepvec)

Talimogene laherparepvec is an attenuated herpes simplex virus type 1 (HSV-1) [redacted] M-CSF recruits and activates antigen presenting cells which can process and present tumor-derived antigens to promote an effector T-cell response.

2.2.1.1 Clinical Pharmacokinetics (PK) and Activity of talimogene laherparepvec

Talimogene laherparepvec was approved for intratumoral injections in cutaneous, subcutaneous and/or nodal lesions at the following dose and schedules:

- 1st dose at 10^6 PFU/mL for a maximum volume of 4mL
- 2nd dose 3 weeks later at 10^{8}PFU/mL for a maximum of 4mL

All subsequent doses will be provided every two weeks at 10^{8}PFU/mL for a maximum of 4 mL per treatment cycle

Pharmacokinetics of talimogene laherparepvec
The biodistribution and shedding of intralesionally administered talimogene laherparepvec are being investigated in an ongoing study measuring talimogene laherparepvec DNA and virus in blood, oral mucosa, urine, injection site, and occlusive

dressings. [redacted]

Antitumor Activity:
Talimogene laherparepvec demonstrated initial biological activity as monotherapy in subjects with advanced solid tumors with metastases in the skin or subcutaneous (SC) tissue as evidenced by necrosis or apoptosis in tumor biopsies (Study 001/01).

In a phase III trial in melanoma (Study 005/05 "A Randomized Phase 3 Clinical Trial to Evaluate the Efficacy and Safety of treatment with OncoVEX^{GM-CSF} Compared to Subcutaneously Administered GM-CSF in Melanoma Patients with Unresectable Stage IIIb, IIIc and IV Disease"), talimogene laherparepvec demonstrated an improvement in the primary endpoint, durable response rate (DRR) (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): 16.3% vs. 2.1%. Overall survival (OS) was a secondary endpoint. At the primary analysis, median OS was 23.3 (95% confidence interval [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 talimogene laherparepvec compared with GM-CSF (23.3 vs 18.9 months; 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.

Response to talimogene laherparepvec can be delayed, and the phenomenon sometimes referred to as "pseudoprogression" has been observed. In the pivotal clinical trial, the median time to response onset was 4.1 months (ranged from 1.2 to 16.7 months). Approximately 50% of the patients ultimately achieved a response had evidence of increase in the size of existing lesions and/or development of new lesions. Pseudoprogression can also be seen with other immunotherapies. Patients may continue treatment if there was increase in the size of existing lesions or development of new lesions, as long as the investigator determined that initiation of a new treatment was not required.

2.2.1.2 Talimogene laherparepvec Safety Profile

As of a June 30, 2015 data cutoff, 486 subjects have received talimogene laherparepvec (with doses from 10^4 to 10^8 PFU/mL) and have provided safety data across 15 studies (Investigator's Brochure, 2015). Thirty-one of these subjects continued into the extension phase of two of these studies; a detailed summary of safety results is available in Table 6-3 of the Talimogene laherparepvec Investigator's Brochure (2015).

Overall, most adverse events (AEs) reported in subjects administered talimogene laherparepvec are non-serious and primarily include flu-like symptoms and injection site reactions (Investigator's Brochure, 2015). Most fatal AEs reported in subjects administered talimogene laherparepvec were reported in the setting of disease progression. In the phase 3 study (005/05), the three most frequent AEs observed in the talimogene laherparepvec group were fatigue (36.2% GM-CSF, 50.3% talimogene laherparepvec), chills (8.7%, 48.6%), and pyrexia (8.7%, 42.8%). The following table also include AEs that occurred with a higher incidence in the talimogene laherparepvec group compared with the GM-CSF group.

AEs Reported with At Least a 5% Greater Incidence in Patients Treated with talimogene laherparepvec vs. GM-CSF*
(based on phase 3 trial of talimogene laherparepvec vs. GM-CSF in unresectable melanoma)

Adverse reactions	**Talimogene Laherparepvec talimogene laherparepvec(n=292)**		**GM-CSF (n=127)**	
	Any Grade n (%)	**Grade 3 n (%)**	**Any Grade n (%)**	**Grade 3 n (%)**
General disorders and administrative site conditions				
Fatigue	147 (50.3)	6 (2.1)	46 (36.2)	1 (<1)
Chills	142 (48.6)		11 (8.7)	
Pyrexia	125 (42.8)		11 (8.7)	
Influenza-like illness	89 (30.5)	2 (<1)	19 (15.0)	
Injection site pain	81 (27.7)	2 (<1)	8 (6.3)	
Gastrointestinal disorders				
Nausea	104 (35.6)	1 (<1)	25 (19.7)	
Vomiting	62 (21.2)	5 (1.7)	12 (9.5)	
Diarrhea	55 (18.8)	1 (<1)	14 (11.0)	
Constipation	34 (11.6)		8 (6.3)	1 (<1)
Abdominal pain	26 (8.9)	2 (<1)	3 (2.4)	
Musculoskeletal and connective tissue disorders				
Myalgia	51 (17.5)	1 (<1)	7 (5.5)	
Arthralgia	50 (17.1)	2 (<1)	11 (8.7)	
Pain in extremity	48 (16.4)	4 (1.4)	12 (9.5)	1 (<1)
Nervous system disorders				
Headache	55 (18.8)	2 (<1)	12 (9.5)	
Dizziness	28 (9.6)		4 (3.2)	
Respiratory, thoracic, and mediastinal disorders				
Oropharyngeal pain	17 (5.8)		1 (<1)	
Investigations				

Weight decreased	17 (5.8)	1 (<1)	1 (<1)	
*Other adverse reactions associated with talimogene laherparepvec in the open-label, randomized study includes glomerulonephritis, vitiligo, cellulitis, and oral herpes.				

2.2.1.2.1 Important Identified Risks with talimogene laherparepvec:

1) Injection site reactions: Talimogene laherparepvec has been injected into cutaneous, subcutaneous and nodal tumor lesions. Injection site reactions may include erythema, discoloration, induration and pain. Necrosis at injected site may also occur.
2) Cellulitis at site of injection: Intralesional administration of talimogene laherparepvec has been associated with cellulitis at the injection site, and systematic infection may develop. In the phase 3 melanoma clinical study, the incidence of AEs in the bacterial cellulitis category was 6.2% in the talimogene laherparepvecgroup (vs. 1.6% in the GM-CSF group).
3) Impaired wound healing at site of injection: Impact healing at the injection site has been reported, and the risk may be increased in settings with underlying risk factors (e.g. previously radiated or poorly vascularized areas). One patient with peripheral vascular disease had an amputation of lower extremity due to infection of non-healing wound after talimogene laherparepvec injection. In the phase 3 melanoma clinical study, the impaired wound healing occurred in 5.5% of patients in the talimogene laherparepvec group (vs. 2.4%) in the GM-CSF group.
4) Immune-mediated AEs: Across melanoma studies, immune-mediated adverse events considered possibly related to talimogene laherparepvec were reported in 2% of subjects treated with talimogene laherparepvec (and included events of vasculitis, glomerulonephritis, acute renal failure, pneumonitis, and worsening psoriasis. Most cases were grade 2 or 3. One grade 4 case (glomerulonephritis) was reported, which resolved with treatment, and no fatal cases were reported. Other contributory factors were identified in several of these cases, including pre-existing immune-mediated conditions, other concurrent medications, and intercurrent medical events.
5) Plasmacytoma at the injection site: A case was reported in the phase 3 melanoma clinical study. The plasmacytoma developed the area of the injected tumor on the scalp after 9 cycles of treatment with talimogene laherparepvec. On medical review, the event was felt to be consistent with recruitment of plasma cells in response to the talimogene laherparepvec injections and the patient had a pre-existing (smoldering) multiple myeloma. This case was considered possibly related to the treatment. No other cases of plasmacytoma have been reported in clinical trials with talimogene laherparepvec to date.
6) Obstructive airway disorder: In the phase 3 melanoma clinical study (005/05), one (0.3%) subject treated with talimogene laherparepvec reported the adverse event of obstructive airways disorder. The event was grade 4 and resolved with sequelae. The female subject was previously treated with high-dose interleukin-2 and experienced

an acute respiratory failure requiring intubation. The subject complained of breathing problems after discharge. Four to 6 weeks later, she received the first dose of talimogene laherparepvec (two 1 - 1.5 cm lesions in the right supraclavicular fossa). Thirteen days after the second talimogene laherparepvec dose, the subject presented with acute respiratory distress requiring an emergency tracheostomy. Imaging showed a mass in the larynx on the contralateral side and adjacent lymph node. Etiology of the laryngeal mass was unclear. A temporal relationship to talimogene laherparepvec treatment was present. Study medication was permanently discontinued

7) Disseminated herpetic infection in SEVERELY immunocompromised individuals (defined as those with any severe congenital or acquired cellular and/or humoral immune deficiency): talimogene laherparepvec has not been studied in immunocompromised patients. However, based on animal data (see Section 5.2 of IB), patients who are severely immunocompromised (*e.g.*, patients with severe congenital or acquired cellular and/or humoral immune deficiency) may be at an increased risk of disseminated herpetic infection and should not be treated with talimogene laherparepvec. "Disseminated herpetic infection in severely immunocompromised individuals" is defined as an important identified risk based on preclinical toxicology with talimogene laherparepvec as well as clinical observations of wild-type HSV-1 infection in immunocompromised patients. In preclinical studies in 100% SCID mice (devoid of T and B cells) and 20% BALB/c nude mice (deficient in T cells and partially deficient in B cell function), viral inclusion bodies and necrosis were observed in multiple organs, including neurons of the GI tract, adrenal gland, eyes, skins and brain.

8) Deep vein thrombosis

2.2.1.2.2 Important Potential Risks with talimogene laherparepvec:

1) Disseminated herpetic infection in immunocompromised individuals (***defined*** as those with HIV/ AIDS, leukemia, lymphoma, common variable immunodeficiency, or those who require high-dose steroids or other immunosuppressive agents): Note, for patients who are severely immunocompromised (completely lacking T with complete or partially impaired B cell function), disseminated herpetic infection is an "identified" AE (see section of talimogene laherparepvec Identified Risks. It is unknown whether patients who are not severely immunocompromised (those with conditions limited to T cell dysfunction such as HIV, AIDS, or patients with common variable immunodeficiency or those who require chronic treatment with steroids or other immunosuppressive agents) are at increased risk. The potential risk of disseminated herpetic infection and the potential benefits of treatment should be considered before administering talimogene laherparepvec to these patients.

2) Symptomatic talimogene laherparepvec infection in normal tissues: In mouse tumor models, viral lysis/tissue injury was limited to tumors in immunocompetent animals. There was no clinical or pathological evidence of symptomatic infection or injury to

normal tissues after repeated intratumoral, intravenous, or subcutaneous injection, including mice dosed with up to 10^7 PFU talimogene laherparepvec (~60-fold over the highest proposed clinical dose, on a PFU/kg basis) via weekly subcutaneous injection for up to 3 months.

No human cases of confirmed infection of non-tumor tissues by talimogene laherparepvec have been reported. While 5.5% of patients treated with talimogene laherparepvec (vs 1.6% in the BM-CSF group) reported oral or corneal herpes infection, it is not confirmed whether the source was wide-type herpes or talimogene laherparepvec. Patients who develop herpes-like lesions should follow stand hygienic practice to prevent viral transmission.

3) Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type HSV-1: Co-infection of neurons already harboring latent wild-type HSV-1 by talimogene laherparepvec could potentially stimulate the reactivation of latent wild-type HSV-1 in patients with prior infection.

   Talimogene laherparepvec infection of tumor or non-tumor tissues could potentially lead to establishment of latency and subsequent reactions of talimogene laherparepvec if the virus comes into contact with axonal nerve terminals and was transported to neuronal cell bodies. In mice, biodistribution studies have detected low levels of talimogene laherparepvec in trigeminal ganglia through 28 days in 1 of 6 animals following high-dose IV administration (0.6 × 107 PFU, ~36-fold over the highest proposed clinical dose). Talimogene laherparepvec was undetectable in trigeminal ganglia in mice after subcutaneous administration.

4) Recombination of talimogene laherparepvec with wild-type HSV-1: This event has not been reported in the phase 3 melanoma clinical study. The genetic modifications made to talimogene laherparepvec only attenuate the virus, either by limiting replication to tumor cells and neurovirulence (by deletion of ICP34.5) or enhancing immune detection of infected cells (by eliminating ICP47), none of the theoretical products of recombination between wild-type HSV-1 and talimogene laherparepvec would have increased virulence. The likelihood of recombination occurring is low, and if recombination occurred, the virulence of the recombinants would be no greater than wild-type HSV-1, and symptoms will be reduced compared to wild-type HSV-1. Management with systemic antivirals would be the same.

5) Talimogene laherparepvec-mediated anti-GM-CSF antibody response: There is a theoretical concern that transgene-derived expression of GM-CSF could induce an immune response reactive with endogenous GM-CSF. Autoantibodies against GM-CSF is detected in 9.6% general population. It is not known whether such phenomena could be expected with the limited exposure anticipated with transgene expression of GM-CSF from talimogene laherparepvec.

2.2.1.2.3 Special Precautions:

1) Accidental exposure of healthcare providers (HCP) to talimogene laherparepvec: A needle stick injury, spill, or splash back during administration may result in accidental exposure of healthcare providers (HCPs) to talimogene laherparepvec. The ICP34.5 gene deletion is intended to allow only tumor selective replication and limited or no viral replication in normal tissues. The signs or symptoms of primary infection at the site of exposure are expected to be similar to what is seen with wild-type HSV-1. The severity of symptoms is expected to be reduced compared to what is seen with wild-type HSV-1. Talimogene laherparepvec is sensitive to acyclovir. In one case of exposure of study personnel to talimogene laherparepvec, the exposed physician developed clinical signs of a herpetic whitlow-like lesion at the site of an accidental needle stick that resolved after treatment with acyclovir.
2) Transmission of talimogene laherparepvec from patient to close contacts or HCPs via direct contact with infected lesions or body fluids resulting in symptomatic infection (primary or reactivation): A clinical study is in progress to inform whether talimogene laherparepvec is present in saliva or oral or genital secretions of treated patients. The likelihood of transfer of talimogene laherparepvec to a close contact or HCP increases if the contact has a break in the skin or mucous membranes. Signs or symptoms of infection would be anticipated to be similar to signs and symptoms of wild-type HSV infection, although the reduced potential to replicate in normal tissue may result in less severe clinical manifestations. Shedding results showed that talimogene laherparepvec was detected on the surface of injected lesions for up to 2 weeks after injection in 8 of 72 (11%) subjects. Virus was not detected on the exterior surface of tumor dressings at any time point tested.

2.1.2.2.4 Loss of efficacy in patients treated with systemic acyclovir:

Talimogene laherparepvec retained an intact thymidine kinase gene, and is therefore sensitive to acyclovir and acyclovir may attenuate activity of talimogene laherparepvec. The risks and benefits of talimogene laherparepvec treatment before administering acyclovir or other anti-viral agents indicated for management of herpetic infection will need to be considered. Other treatments, such as foscarnet, may be used as an alternative for acyclovir.

2.3 *Other Agent(s)*

5-Fluorouracil (5-FU; fluorouracil)

Chemically, fluorouracil, a fluorinated pyrimidine, is 5-fluoro-2,4 (1H,3H)-pyrimidinedione.

Clinical Pharmacology and Pharmacokinetics:

Following intravenous injection, fluorouracil distributes into tumors, intestinal mucosa, bone marrow, liver and other tissues throughout the body. In spite of its limited lipid solubility, fluorouracil diffuses readily across the blood-brain barrier and distributes into cerebrospinal fluid and brain tissue. Seven to 20 percent of the parent drug is excreted unchanged in the urine in 6 hours; of this, over 90% is excreted in the first hour. The remaining percentage of the administered dose is metabolized, primarily in the liver. The catabolic metabolism of fluorouracil results in degradation products (e.g., CO2, urea and α-fluoro-ß-alanine) which are inactive. The inactive metabolites are excreted in the urine over the next 3 to 4 hours. When fluorouracil is labeled in the six carbon position, thus preventing the 14 C metabolism to CO2, approximately 90% of the total radioactivity is excreted in the urine. When fluorouracil is labeled in the two carbon position, approximately 90% of the total radioactivity is excreted in expired CO2. Ninety percent of the dose is accounted for during the first 24 hours following intravenous administration.Following intravenous administration of fluorouracil, the mean half-life of elimination from plasma is approximately 16 minutes, with a range of 8 to 20 minutes, and is dose dependent. No intact drug can be detected in the plasma 3 hours after an intravenous injection.

Toxicity
Nausea, diarrhea, vomiting (mild); stomatitis: 5-8 days after treatment initiation; myelosuppression: granulocytopenia (9-14 days); thrombocytopenia (7-14 days); alopecia; loss of nails; hyperpigmentation; photosensitivity; maculopapular rash; palmar–plantar erythrodysethesias: (42-82% receiving continuous infusion); CNS effects: cerebral ataxia (rare); cardiotoxicity: infarction, angina; asymptomatic S–T changes 68%; ocular effects: excessive lacrimation and less commonly, tear duct stenosis.

Drug Interaction
Concomitant administration of 5-FU with warfarin has been reported to result in increased INR/prolonged prothrombin time. Patients receiving both drugs should be followed with weekly INRs.

2.3.1 Oxaliplatin (Eloxatin)

Oxaliplatin is an antineoplastic agent with the molecular formula C8H14N2O4Pt and the chemical name of *cis*-[(1 *R*,2*R*)-1,2-cyclohexanediamine-*N*,*N*'] [oxalato(2-)- *O*,*O*'] platinum. The molecular weight is 397.3. Oxaliplatin is slightly soluble in water at 6 mg/mL, very slightly soluble in methanol, and practically insoluble in ethanol and acetone.

Clinical Pharmacology and Pharmacokinetics:
Oxaliplatin undergoes nonenzymatic conversion in physiologic solutions to active derivatives via displacement of the labile oxalate ligand. Several transient reactive species are formed, including monoaquo and diaquo DACH platinum, which covalently bind with macromolecules. Both inter- and intrastrand Pt-DNA crosslinks are formed. Crosslinks are formed between the *N7* positions of two adjacent guanines (GG), adjacent adenine-guanines (AG), and guanines separated by an

intervening nucleotide (GNG). These crosslinks inhibit DNA replication and transcription. Cytotoxicity is cell-cycle nonspecific.

The reactive oxaliplatin derivatives are present as a fraction of the unbound platinum in plasma ultrafiltrate. Pharmacokinetic parameters obtained after a single 2-hour intravenous infusion of oxaliplatin at a dose of 85 mg/m2 expressed as ultrafilterable platinum were Cmax of 0.814 mcg/mL and volume of distribution of 440 L. Interpatient and intrapatient variability in ultrafilterable platinum exposure (AUC0−48hr) assessed over 3 cycles was moderate to low (23% and 6%, respectively).

Distribution

At the end of a 2-hour infusion of oxaliplatin, approximately 15% of the administered platinum is present in the systemic circulation. The remaining 85% is rapidly distributed into tissues or eliminated in the urine. In patients, plasma protein binding of platinum is irreversible and is greater than 90%. The main binding proteins are albumin and gamma-globulins. Platinum also binds irreversibly and accumulates (approximately 2-fold) in erythrocytes, where it appears to have no relevant activity. No platinum accumulation was observed in plasma ultrafiltrate following 85 mg/m2every two weeks.

Metabolism

Oxaliplatin undergoes rapid and extensive nonenzymatic biotransformation. There is no evidence of cytochrome P450-mediated metabolism *in vitro*.

Up to 17 platinum-containing derivatives have been observed in plasma ultrafiltrate samples from patients, including several cytotoxic species (monochloro DACH platinum, dichloro DACH platinum, and monoaquo and diaquo DACH platinum) and a number of noncytotoxic, conjugated species.

Elimination

The major route of platinum elimination is renal excretion. At five days after a single 2-hour infusion of oxaliplatin, urinary eliminate accounted for about 54% of the platinum eliminated, with fecal excretion accounting for only about 2%. Platinum was cleared from plasma at a rate (10 − 17 L/h) that was similar to or exceeded the average human glomerular filtration rate (GFR; 7.5 L/h). There was no significant effect of gender on the clearance of ultrafilterable platinum. The renal clearance of ultrafilterable platinum is significantly correlated with GFR.

Clinical Studies

Adjuvant Therapy of Colorectal Cancer

The benefit for adding oxaliplatin to 5-FU/leucovorin (LV) was first demonstrated in the MOSAIC trial that randomized 2246 patients with resected stage II (40%) or III colon cancer to infusional 5-FU with (FOLFOX) or without oxaliplatin. After a median follow-up of 82 months, 5-year disease free survival (DFS) was significantly higher with FOLFOX (73% vs 67%, hazard ratio, HR 0.80). Six-year overall survival rates were significantly higher, both in the entire group (79 versus 76 percent, HR 0.84, p = 0.046), and in those with stage III (73 versus 69 percent, HR 0.80, p = 0.023), but not stage II disease. The survival benefit of oxaliplatin was maintained with long-term follow-up in those with stage III disease (10-year overall survival 67 versus 59 percent; HR 0.80, p = 0.016) but not stage II disease (10-year survival 78 versus 80 percent)[12, 13].

The NSABP-C07 trial assigned 2407 patients with stage II (29 percent) or III colon cancer to bolus weekly FU/LV with (FLOX) or without oxaliplatin for 6 months. With eight years of median follow-up, five-year DFS significantly favored FLOX (69 versus 64 percent, HR 0.82). Based on these results, oxaliplatin was approved for adjuvant therapy of resected stage III colon cancer. Since toxicities in the NSABP-C07 trial was significantly higher due to bolus FU/LV, FOLFOX regimen with infusional 5-FU is preferred[14].

The combination of capecitabine plus oxaliplatin (XELOX), was compared with bolus FU/LV in a phase III trial involving 1886 patients with stage III colon cancer. In the latest report, after a median followup of 74 months, DFS was significantly superior with XELOX than with bolus FU/LV (HR for DFS 0.80, 95% CI 0.69-0.93, seven-year DFS of 63 versus 56 percent), as was overall survival (HR 0.83, 95% CI 0.70-0.99, seven-year overall survival 73 versus 67 percent)[8].

Additional support for the substitution of capecitabine for FU when used in combination with oxaliplatin comes from a pooled analysis of four randomized trials examining a variety of adjuvant strategies in patients with stage III colon cancer. Combination therapy with oxaliplatin provided consistently improved outcomes irrespective of whether the fluoropyrimidine backbone was capecitabine or FU/LV[15].

Although there are no completed randomized, phase III trials evaluating the benefit of adjuvant adding oxaliplatin to adjuvant 5FU/LV following fluoropyrimidine-based chemoradiation in rectal cancer, safety of this approach was established by the E3201 trial[16]. The randomized phase II ADORE trial that randomly assigned 321 patients with resected rectal cancer following neoadjuvant chemoradiation to FOLFOX or FU/LV showed higher three-year DFS (72% vs 63%)[17]. Based on these results and extrapolating data from resected colon cancer, consensus guidelines including those from NCCN include oxaliplatin with a fluoropyrimidine as options.

Toxicity

The most commonly observed oxaliplatin toxicities include neurotoxicity, GI toxicity, and myelosuppression. Three neurotoxicity syndromes have been seen: acute sensory neuropathy develops within hours to 2 days after oxaliplatin administration. Symptoms include paresthesias, dysesthesias, and hypothesia of the hands, feet and perioral region. Jaw spasm, abnormal tongue sensation, dysarthria, eye pain and a sensation of chest pressure have also been noted. Acute sensory neuropathy symptoms may be exacerbated by exposure to cold temperature or cold

objects. Symptoms are reversible, usually resolving within 14 days and commonly recurring with further dosing. This syndrome has been observed in about 56% of patients receiving oxaliplatin with 5-FU and leucovorin.

Acute pharyngolaryngeal dysesthesia is reported to occur in 1-2% of patients. This syndrome is characterized by a subjective sensation of difficulty breathing or swallowing without laryngospasm or bronchospasm or objective evidence of hypoxia. Avoidance of cold drinks, food and air is suggested in order to minimize pharyngolaryngeal dysesthesia. Antianxiety agents (e.g., lorazepam) may be used to treat pharyngolaryngeal dysesthesias once oxygen saturation has been documented to be normal.

Peripheral neuropathy persisting > 14 days is characterized by paresthesias, dysesthesias, and hypothesia. Abnormalities in proprioception may also be seen. Symptoms of persistent neuropathy may improve upon discontinuation of oxaliplatin.

Gastrointestinal toxicities include nausea, vomiting (oxaliplatin is considered to be moderately emetogenic) and diarrhea.

Neutropenia is reported in 73% of patients receiving oxaliplatin with 5-FU and leucovorin (44% grade 3 or 4). Grade 3 or 4 thrombocytopenia is reported to occur in 4% of patients receiving the combination.

Allergic reactions, similar to those seen with other platinum compounds, have also been observed in patients treated with oxaliplatin. Reactions range from rash to anaphylaxis.

Rarely, oxaliplatin has been associated with pulmonary fibrosis, which may be fatal. Oxaliplatin should be discontinued in the presence of unexplained pulmonary symptoms (e.g. nonproductive cough, dysphagia) or pulmonary infiltrates until interstitial lung disease or pulmonary fibrosis have been ruled out.

Recent reports of oxaliplatin extravasation suggest that tissue necrosis may result and that oxaliplatin should be considered a vesicant. No standard treatment exists for oxaliplatin extravasation although heat and sodium thiosulfate have both been suggested.

Veno-occlusive disease (VOD) of the liver is a rare complication associated with oxaliplatin and 5-FU. Clinical manifestations of VOD include hepatomegaly, ascites, and jaundice. Histologically, VOD is characterized by diffuse damage in the centrilobular zone of the liver.

Sequelae of VOD include hepatomegaly, splenomegaly, portal hypertension, and esophageal varices. A recent analysis of resected liver metastases in 153 patients indicated histological findings consistent with VOD in 6/27 patients who received 5-FU alone, 4/17 patients who received 5-FU and irinotecan, 20/27 patients who received 5-FU and oxaliplatin, and 14/16 who received 5-FU, oxaliplatin and irinotecan. The remaining 66 patients had not received chemotherapy prior to resection. There were no such findings in these patients.

2.4 **Rationale for Proposed Starting Dose and Amendment:**

Talimogene laherparepvec is currently FDA approved for advanced melanoma based on a phase III trial in 436 patients with advanced, unresectable melanoma randomized 2:1 to talimogene laherparepvec vs GM-CSF and overall demonstrated its safety. For talimogene laherparepvec and GM-CSF, respectively, incidence of treatment-related grade 3 or 4 AEs was 11% and 5%. The only grade 3 or 4 AE occurring in ≥ 2% of talimogene laherparepvec–treated patients was cellulitis; there were no treatment-related deaths. The rate of discontinuation as a result of AEs was 4% and 2% with talimogene laherparepvec and GM-CSF. This trial establishes the safety profile of talimogene laherparepvec as a single agent.

Talimogene laherparepvec has also been evaluated in combination with chemoradiotherapy in patients with squamous cell cancer of the head and neck (SCCHN). In this trial, patients with stage III/IVA/IVB SCCHN received chemoradiotherapy (70 Gy/35 fractions with concomitant cisplatin 100 mg/m2 on days 1, 22, and 43) and dose-escalating TALIMOGENE LAHERPAREPVEC (10^6, 10^6, 10^6, 10^6 pfu/mL for cohort 1; 10^6, 10^7, 10^7, 10^7 for cohort 2; 10^6, 10^8, 10^8, 10^8 for cohort 3) by intratumoral injection on days 1, 22, 43, and 64. Patients underwent neck dissection 6 to 10 weeks later. Primary end points were safety and recommended dose/schedule for future study. **All (17) patients were treated without delays to chemoradiotherapy or dose-limiting toxicity.** All patients experienced at least one treatment-emergent adverse event (AE): 86% were grade 1 or 2, but at least one grade 3 or 4 AE was observed in each patient. However, the investigators considered just two adverse events (pyrexia and fatigue) to be talimogene laherparepvec related and occurred in two or more patients. Across all cohorts and severity grades, the most frequent AEs were consistent with chemoradiation. Talimogene laherparepvec has also successfully been evaluated in 17 patients with pancreatic adenocarcinoma in combination with chemoradiation and similar to previously reported experience, most adverse events were non-serious and primarily included flu-like symptoms and injection site reactions. Most serious events were reported in setting of disease progression[18]. Based on these data, and upon recommendations from CTEP, we initiated the trial with escalating doses of TVEC in combination with capecitabine based chemoradiation as below.

Dose level	**Talimogene laherparepvec Dose (PFU/ml)**	**Capecitabine (mg/m^2 po bid on days of radiation)**	**Radiation**
1	10^6, 10^7, 10^7,10^7	825	50.4 gray in 28 fractions
2	10^6, 10^8, 10^8,10^8	825	50.4 gray in 28 fractions

Talimogene laherparepvec was administered via endoscopy by a qualified physician for a total of 4 doses at the following time points: a) week 1 prior to initiation of FOLFOX chemotherapy b) weeks 2-4 during FOLFOX chemotherapy c) week 6 d) week 8-9 during chemoradiation.

Enrollment to the first cohort was completed without any DLTs, treatment related SAEs or dose interruptions. TVEC was delivered safely without any local reactions being experienced by patients and all patients underwent surgery.

Subsequently the protocol was amended to replace chemoradiation with short course radiation based on emerging data from ASCO 2020 and shifting practice patterns post COVID. The RAPIDO trial was an investigator-driven, open-label, randomized, controlled, phase 3 trial in patients with locally advanced rectal cancer classified as high risk based on pelvic MRI (with at least one of the following criteria: clinical tumor [cT] stage cT4a or cT4b, extramural vascular invasion, clinical nodal [cN] stage cN2, involved mesorectal fascia, or enlarged lateral lymph nodes). Patients allocated to the experimental treatment group received short-course radiotherapy (5 × 5 Gy over a maximum of 8 days) followed by chemotherapy with fluoropyrimidine and oxaliplatin for up to 18 weeks followed by total mesorectal excision. Patients allocated to the standard of care group received long course chemoradiation up to 50·4 Gy concomitant twice-daily oral capecitabine 825 mg/m^2 followed by total mesorectal excision and, if stipulated by hospital policy, adjuvant chemotherapy with eight cycles of CAPOX or 12 cycles of FOLFOX4. Median follow-up was 4·6 years. At 3 years after randomization, the cumulative probability of disease-related treatment failure, the primary endpoint was 23·7% (95% CI 19·8–27·6) in the experimental group versus 30·4% (26·1–34·6) in the standard of care group (hazard ratio 0·75, 95% CI 0·60–0·95; p=0·019). Serious adverse events occurred in 177 (38%) of 460 participants in the experimental group and, in the standard of care group, in 87 (34%) of 254 patients without adjuvant chemotherapy and in 64 (34%) of 187 with adjuvant chemotherapy.

This trial thus established the efficacy and safety of short course radiation.
During the COVID pandemic, with an intent towards reducing patient time in health care settings, short course radiation has been recommended by multiple consensus guidelines, was rapidly implemented across the country and is now standard of care for locally advanced rectal cancer patients. The protocol will be amended to replace chemoradiation with short course radiation for dose level 2 as below.

Dose level	**Talimogene laherparepvec Dose (PFU/ml)**	**Capecitabine (mg/m^2 po bid on days of radiation)**	**Radiation**
1	10^6, 10^7, 10^7,10^7	825	50.4 gray in 28 fractions
1 (amended)	1x 10^6, 1x 10^7, 1x 10^7,1x 10^7	N/A	25 Gray in 5 fractions (To be implemented if DLTs noted with DL2)
2 (amended)	10^6, 10^8, 10^8,10^8	N/A	25 Gy in 5 fractions

Talimogene laherparepvec will be administered via endoscopy by a qualified physician for a total of 4 doses as before but at the following amended time points: a) week 1 prior to initiation of FOLFOX chemotherapy b) weeks 3, 5 and 7 during FOLFOX chemotherapy.

In addition to monitoring patients for AEs related to talimogene laherparepvec, injection site will be evaluated directly during endoscopy at subsequent time points such as during pre-surgical evaluation and in those forgoing surgery needing endoscopic surveillance.

2.5 **Rationale**

The current standard of care for resectable rectal cancer is neoadjuvant therapy typically with 45 Gray (Gy) + 5.4 Gy boost over 28 fractions along with concomitant capecitabine (825 mg /m2 by mouth twice daily) or infusional 5-FU 300 mg /m2 on days of radiation followed by total mesorectal excision surgery 6-8 weeks post-completion of neoadjuvant therapy. Following recovery from surgery, further fluoropyrimidine based adjuvant chemotherapy (5-FU or capecitabine with or without oxaliplatin) for 4-5 months is recommended to decrease risk of distant metastatic recurrence. However, with this approach, the pathological complete response rates continue to be low (15-20%), the rates of distant relapse high (up to 40% - 50% in high risk sub groups) and all patients experience morbidities related to surgery. Multiple attempts to further improve outcomes in the neoadjuvant setting by adding other agents active in the metastatic setting to either 5-FU or capecitabine including oxaliplatin, irinotecan, cetuximab, ziv-aflibercept have all largely been unsuccessful.

In contrast, talimogene laherparepvec -based oncolytic viral therapy in combination with neoadjuvant chemoradiation holds great promise in the management of rectal adenocarcinoma. Firstly, oncolytic viruses may show natural selectivity for cancers with an over-active RAS signaling pathway thus making colorectal cancer an attractive target[19]. It is well established that the majority of colorectal cancers have activated RAS signaling through various mechanisms including overexpression of epidermal growth factor receptor (EGFR) ligands, mutations in RAS, RAF genes and other mechanisms. The PKR pathway inhibits protein translation, production of viral particles and thus spread of the virus. However, RAS-transformed cancer cells do not initiate the PKR pathway, rendering them more susceptible to oncolytic viruses. In the case of attenuated HSV oncolytic viruses, deletions of ICP34.5 and US11 genes results in preferential lysis of cells with defective PKR signaling i.e. cells with activated RAS [19, 20].

Secondly, strong evidence also points towards synergy of oncolytic viruses with current standard of care of fluoropyrimidine-based chemoradiation. In a preclinical study of oncolytic HSV2 in 4 CRC cell lines (HT-29, LoVo, HCT116 and SW620), oncolytic viruses were found to be highly cytotoxic and showed significant synergy with 5-FU. These results were also replicated in cell line xenograft models with increased tumor inhibiton, longer survival without increased toxicity compared to 5-FU alone [21].

Finally, growing evidence suggests that radiation-induced cancer cell death is immunogenic resulting in numerous immune modulatory effects in the tumor microenvironment including a) improvement of T-cell, dendritic cell recruitment and infiltration into the tumor b) upregulation of major histocompatibility class-1 (MHC-1) ligands on cancer cells leading to increased recognition and killing by CD8+ T cells[22]. In a phase I study of talimogene laherparepvec and radiation with cisplatin-based chemoradiation in SCCHN, 14 / 17 patients had tumor response by RECIST criteria and pathologic complete remission was confirmed in 93% of patients at neck dissection. No patient developed locoregional recurrence, and disease-specific survival was 82.4% at a median follow-up of 29 months (range, 19-40 months). Of particular interest is the extremely high (94%) pathologic complete response rate and the fact that no locoregional relapses have occurred. These values exceed those in historical control series, in which rates of

60% to 71% for histopathologic complete response and 30% to 50% for two-year locoregional relapse are typical[20].

Therefore, in the current study, we propose to evaluate the synergistic potential of talimogene laherparepvec in combination with radiation and chemotherapy in rectal cancer.

2.6 **Correlative Studies Background**

2.6.1 Neoadjuvant Rectal Score

2.6.1.1 Rationale

The NAR score has been validated in clinical trials as a surrogate endpoint for overall survival. The score is designed to be particularly sensitive to changes in factors that are affected by neoadjuvant therapy.

2.6.1.2 Background

NAR is calculated based on the clinical T stage (cT), pathological T (pT) and pN stages as:

$$NAR = [5pN- 3 (cT- pT) + 12]^2 / 9.61.$$

The NAR score has been validated in the randomized NSABP R04 study which evaluated four different fluoropyrimidine-based radioensitizing regimens in 1479 patients with resectable rectal cancer. NAR score in this dataset was significantly associated with overall survival, OS as both a continuous variable (HR/unit 1.04; 95% CI 1.03 – 1.05; $p < 0.0001$) and when the observed scores were categorized into tertiles ($p < 0.0001$). The NAR score was subsequently and independently further validated in an international clinical trial dataset providing further evidence of utility as a short-term surrogate marker[23]. NAR is being used as the primary end point of the proposed randomized phase II modular NCTN clinical trial platform utilizing Total Neoadjuvant Therapy (TNT) with parallel experimental arms in LARC (Nrg-GI002).

2.6.1.3 Hypothesis

We hypothesize that talimogene laherparepvec based neoadjuvant therapy will result in an improvement in the NAR score. We recognize that the small sample size and lack of control arm prevent definitive conclusions but the findings will be compared to historical controls and will serve as the preliminary data for designing future, larger trials

2.6.2 MRI-based determinants of response, DFS and OS

2.6.2.1 Rationale

Pelvic MRIs are standard of care in the management of resectable rectal cancer to accurately determine stage, evaluate circumferential margins and to determine the extent of required surgery. Emerging data show that baseline MRI features and changes with neoadjuvant therapy correlate with outcomes in patients. However, it is unknown whether pelvic MRIs are able to identify tumor regression with talimogene laherparepvec -based neoadjuvant therapy.

2.6.2.2 Background

In the prospective MERCURY study with a cohort of over 350 patients with resectable rectal cancer, pre-treatment MRI was shown to be predictive of a curative resection based on involvement of the circumferential margin (mrCRM). A subgroup of 111 patients who had both pre- and post-neoadjuvant therapy pelvic MRI were retrospectively evaluated for the prognostic value of tumor regression grade (mrTRG) and mrCRM. Both mrTRG and mrCRM were found to have strong prognostic effects on OS and DFS, as well as for local recurrence (mrCRM only). Based on these data, dedicated pelvic MRIs are performed before and after neoadjuvant therapy in rectal cancer patients routinely as standard of care including at our institution[24].

2.6.2.3 Hypothesis

We hypothesize that rectal adenocarcinoma patients treated with talimogene laherparepvec based neoadjuvant therapy will show improvement in mrCRM involvement and tumor regression and that these changes can be reliably evaluated by pelvic MRIs.

2.6.3 Changes in PD-L1 Expression

2.6.3.1 Rationale

Prior studies have shown that radiation and talimogene laherparepvec can both lead to increase in PD-L1 expression in tumors. However, the changes in PD-L1 expression with talimogene laherparepvec based neoadjuvant therapy in rectal adenocarcinoma remains to be determined.

2.6.3.2 Background

Oncolytic viruses often induce interferon (IFN) release in the local tumor microenvironment, and IFN is known to upregulate PD-L1 expression on tumor cells. In fact, preclinical models have validated this approach and several clinical trials are under way. Similarly, radiation independently increases PD-L1 expression by IFN release and other mechanisms. In a preclinical study utilizing an MC-38 colon carcinoma tumors xenograft mouse model, either talimogene laherparepvec or anti-

PD-1 therapy alone induced modest tumor growth inhibition/tumor regressions of contralateral tumors. Correlative studies showed increase in PD-L1 expression in tumors injected with talimogene laherparepvec. In combination, the talimogene laherparepvec injected tumor displayed 8/10 complete regressions and the distant tumors had 2/10 complete regressions[25].

2.6.3.3 Hypothesis

We hypothesize that rectal adenocarcinoma patients treated with talimogene laherparepvec based neoadjuvant therapy will show increase in PD-L1 expression measured by immunohistochemistry in tumor biopsies as compared to baseline.

2.6.4 Immune Cell Profiling

2.6.4.1 Rationale

Growing evidence suggests that rectal cancer response to neoadjuvant chemo radiation (CRT) depends on tumor microenvironment and host immune response. Densities of tumor infiltrating lymphocytes (TILs) and peripheral lymphocytes have been correlated with response in this setting.

2.6.4.2 Background

Local and distant antitumor immune responses have been reported in preclinical models and previous clinical studies of talimogene laherparepvec, radiation and the combination of both. For instance, recently, the numbers of pre-treatment peripheral blood helper T lymphocytes and cytotoxic T cells have been shown to be independent predictors of response to radiation in rectal cancer patients. Also, talimogene laherparepvec therapy has been shown to increase the percent of percent of PD-L1+ T cells associated with dramatic local responses in xenograft models of CRC. In a phase II study of talimogene laherparepvec in melanoma, biopsy of responding lesions suggested an association between response and presence of interferon γ–producing MART-1–specific CD8+ T cells and reduction in CD4+FoxP3+ regulatory T cells[26].

2.6.4.3 Hypothesis

We hypothesize that the local and systemic immune effects of talimogene laherparepvec may cooperate with neoadjuvant therapy to increase locoregional control in rectal cancer. We propose to quantify changes in a) tumor immune cell infiltration and to characterize subtypes of the immune cells by IHC b) peripheral T cell subpopulations by flow cytometry with talimogene laherparepvec injection and radiation in rectal cancer.

2.6.5 Pharmacodynamic Markers of Talimogene Laherparepvec

2.6.5.1 Rationale

Talimogene laherparepvec has previously been shown to be feasible to be used for injection into multiple tumor types including melanoma, SCCHN and pancreatic cancer. However, the feasibility and efficacy of talimogene laherparepvec delivery into rectal adenocarcinoma remains to be determined. The current trial provides a valuable opportunity to evaluate this.

2.6.5.2 Background

Prior studies have shown that all patients seronegative for HSV strongly seroconvert 3-4 weeks after their first dose that for seropositive patients, trend was an increase in anti-HSV antibody with each injection that eventually plateaued. GM-CSF expression in injected tumors has also been shown to increase post-injection that seemed to be dose related in a phase I study increasing from dose level 10^6 to 10^7. This phase I and other phase II studies have also established talimogene laherparepvec DNA as a reliable marker for talimogene laherparepvec infection and replication within injected lesions.

2.6.5.3 Hypothesis

We hypothesize that endoscopic injection of talimogene laherparepvec into rectal adenocarcinoma is an effective delivery method leading to adequate infection and proliferation of the oncolytic virus within the tumor cells as demonstrated by increase in serum HSV antibody titers (measured by ELISA), GM-CSF (IHC) and talimogene laherparepvec DNA (qRT PCR) in tumor samples

3. PATIENT SELECTION

3.1 **Inclusion Criteria**

3.1.1 **For dose escalation:** Patients must have A) histologically or cytologically confirmed low lying (up to 6 cm of anal verge) rectal adenocarcinoma eligible for radiation therapy to rectal tumor, B) If the treatment is palliative in the metastatic setting, no additional requirements for tumor size or nodal involvement is needed. C) If the treatment is in the neoadjuvant setting, the tumor must ALSO be high-risk locally advanced rectal cancer defined as T3-4, N+, and/or at risk for a positive radial margin (as determined by the surgeon)

3.1.2 **For dose expansion:** Patients must have A) histologically or cytologically confirmed rectal adenocarcinoma eligible for radiation therapy to rectal tumor irrespective of location from anal verge, B) If the treatment is palliative in the metastatic setting, no additional requirements for tumor size or nodal involvement is needed. C) If the treatment is in the neoadjuvant setting, the tumor must ALSO be high-risk locally advanced rectal cancer defined as T3-4, N+, and/or at risk for a positive radial margin (as determined by the surgeon)

3.1.3 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of talimogene laherparepvec in combination with chemotherapy in patients <18 years of age

3.1.4 ECOG performance status ≤ 2 (Karnofsky ≥60%, see Appendix A).

3.1.5 Patients must have normal organ and marrow function as defined below:

- Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
- Hemoglobin ≥9 g/dL
- Platelets ≥100,000 $\times 10^9$/L
- Serum bilirubin ≤1.5x institutional upper limit of normal (ULN) (except patients with Gilbert's Syndrome, who can have total bilirubin < 3 mg/DL)
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5x institutional ULN
- Serum creatinine ≤1.5 mg/dL *OR* calculated creatinine clearance (Cockroft-Gault formula) ≥50 mL/min *OR* 24-hour urine creatinine clearance ≥50 mL/min
- Prothrombin time (PT)/International normalized ratio (INR) and partial thromboplastin time (PTT) ≤1.5x institutional unless the subject is on anticoagulant therapy ((If the subject is receiving anticoagulant therapy, PT, and aPTT must be within therapeutic range of intended use of anticoagulants)

3.1.6 Patients must have signed informed consent indicating that they are aware of the investigational nature of the study, and are aware that participation is voluntary. Patients must be made aware of their other treatment options.

3.1.7 Talimogene laherparepvec, as well as other therapeutic agents used in this trial including radiation and 5-FU, may cause fetal harm when administered to a pregnant woman.

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes.

WOCBP and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, during the study participation, and for four months after the last dose of the drug.

WOCBP must have a negative serum pregnancy test within 72 hours prior to enrollment and agree to use effective contraception throughout the treatment period and for 4 months after the last dose of study treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

3.1.8 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients who have had radiotherapy within < 4 weeks are ineligible.

3.2.2 Patients who have not recovered from adverse events due to prior anti-cancer therapy (*i.e.*, have residual toxicities > Grade 1) except alopecia are ineligible.

3.2.3 Use of other investigational, chemotherapeutic or targeted drugs within 28 days (or five half-lives, whichever is shorter; with a minimum of 14 days from the last dose) preceding the first dose of talimogene laherparepvec and during the study are ineligible.

3.2.4 Patients who have previously been treated with talimogene laherparepvec, any other oncolytic virus or pelvic radiation are ineligible.

3.2.5 Patients with known active central nervous system (CNS) metastases are ineligible.

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.

3.2.6 Patients with a known immediate or delayed hypersensitivity reaction or idiosyncrasy to talimogene laherparepvec or any of its components, 5-FU and / or oxaliplatin are ineligible.

3.2.7 Patients with a history or evidence of active autoimmune disease (*e.g.*, pneumonitis, glomerulonephritis, vasculitis, or other); or history of active autoimmune disease that has required systemic treatment (*i.e.*, use of corticosteroids, immunosuppressive drugs or biological agents used for treatment of autoimmune diseases) within 2 months of enrollment are ineligible. [Replacement therapy (*e.g.*, thyroxine for hypothyroidism, insulin for diabetes or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment for autoimmune disease]

3.2.8 Patients with evidence of clinically significant immunosuppression such as the following are ineligible:
- Primary immunodeficiency state such as Severe Combined Immunodeficiency Disease
- Concurrent opportunistic infection
- Receiving systemic immunosuppressive therapy (>2 weeks) including oral steroid doses >10 mg/day of prednisone or equivalent within 2 months prior to enrollment

3.2.9 Patients with active herpetic skin lesions or prior complications of herpetic infection (*e.g.*, herpetic keratitis or encephalitis) are ineligible.

3.2.10 Patients with viral infections requiring intermittent or chronic systemic (intravenous or oral) treatment with an antiherpetic drug (*e.g.*, acyclovir), other than intermittent topical use are ineligible.

3.2.11 Patients with other viral infections are ineligible:
- Known to have acute or chronic active hepatitis B or hepatitis C infection
- Known to have human immunodeficiency virus (HIV) infection.
- Prior therapy with viral-based tumor vaccine.
- Received live vaccine within 28 days prior to enrollment.

3.2.12 Subject who is unwilling to minimize exposure with his/her blood or other body fluids to individuals who are at higher risks for HSV-1 induced complications such as immunosuppressed individuals, individuals known to have HIV infection, pregnant women, or children under the age of 1 year, during talimogene laherparepvec treatment and through 30 days after the last dose of talimogene laherparepvec are ineligible.

3.2.13 Patients with uncontrolled intercurrent illness including, but not limited to, active, non-colorectal malignancies requiring systemic therapy, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements are ineligible.

3.2.14 Although no effects on embryo-fetal development have been observed in animal studies, adequate and well-controlled studies with talimogene laherparepvec have not been conducted in pregnant women. In addition, given the high risk of detrimental effects of other study agents including 5-FU, oxaliplatin and radiation on embryo-fetal development, the study treatment must be excluded in the following patients:

- Female subject is pregnant or breast-feeding, or planning to become pregnant during study treatment and through 4 months after the last dose of talimogene laherparepvec.
- Female subject of childbearing potential who is unwilling to use acceptable method(s) of effective contraception during study treatment and through 4 months after the last dose of talimogene laherparepvec.
- 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 30 days after treatment with talimogene laherparepvec.

3.2.15 Patients that are unable to swallow oral medications are ineligible

3.2.16 Patients with a major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to initiation of therapy, or anticipation of need for major surgical procedure during the course of the study other than that defined by protocol are ineligible.

3.2.17 Patients with a known DPD deficiency are ineligible

3.2.19 Patients who are unable to get MRIs due to any reason including pacemakers or AICD are ineligible

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

4.1.1 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations require IND sponsors to select qualified investigators. NCI policy requires all persons participating in any NCI-sponsored clinical trial to register and renew their registration annually. To register, all individuals must obtain a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition,

persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN or RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	**IVR**	**NPIVR**	**AP**	**A**
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:.

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the *10058* protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP-IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select *LAO-TX035*, and protocol *#10058.*
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Requirements For 10058 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- For applicable ETCTN studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component. Enrolling sites are responsible for ensuring that the appropriate agreements are in place with their RTI provider, and that appropriate IRB approvals are in place.
- ETCTN Specimen Tracking Training
  - At least one individual at each participating site will need to complete the Theradex-led training
  - Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal
    - The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU.
    - This training will need to be completed before the first patient enrollment at a given site
    - Peter Clark is the main point of contact at Theradex for the training (802-456-8735, PClark@theradex.com). Nafeesa Sarakhawas is the backup contact (609.480.2693, NSarakhawas@theradex.com).

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office

1818 Market Street, Suite 3000

Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.2.4 Checking **Site** Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave. Local Institutional Biosafety Committee (IBC) approval is required before a site can enroll patients to talimogene laherparepvec protocols

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- Have regulatory approval for the conduct of the study at their site.

Prior to accessing OPEN/IWRS, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.

If applicable, all patients have signed an appropriate consent form and HIPAA authorization formOPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.3.3 Special Instructions for Patient Enrollment

The following information will be requested:

- Protocol Number
- Investigator Identification
  - Institution and affiliate name
  - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in Section 3.
- Additional Requirements:
  - Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the ETCTN Biobanking and Molecular Characterization portion of this protocol. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID) and the IWRS-assigned UPID for this trial. **Important: Remove any personally identifying information, including, but not limited to, the patient's name, initials, and patient ID# for this treatment trial, from the institutional pathology report prior to submission.**

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 7 business days.* Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

5.1 Agent Administration (Amended)

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Week 0:

- *Talimogene laherparepvec up to 4 mL of 1x10^6 PFU/mL*

Week 1:

- *5-Fluorouracil (5-FU) 400 mg / m^2 IV bolus followed by*
  5-Fluorouracil (5-FU) 2400 mg / m^2 continuous IV infusion over 46 hours
- *Leucovorin 400 mg /m^2 IV bolus*
- *Oxaliplatin 85 mg/m^2 IV over 2 hours*

Week 3:

- *Talimogene laherparepvec up to 4 mL of 1x10^7 PFU/mL Or 1x10^8 PFU/mL based on assigned dose level*
- *5-Fluorouracil (5-FU) 400 mg / m^2 IV bolus followed by*
  5-Fluorouracil (5-FU) 2400 mg / m^2 continuous IV infusion over 46 hours
- *Leucovorin 400 mg /m^2 IV bolus*
- *Oxaliplatin 85 mg/m^2 IV over 2 hours*

Week 5:

- *Talimogene laherparepvec up to 4 mL of 1x10^7 PFU/mL Or 1x10^8 PFU/mL based on assigned dose level*
- *5-Fluorouracil (5-FU) 400 mg / m^2 IV bolus followed by 5-Fluorouracil (5-FU) 2400 mg / m^2 continuous IV infusion over 46 hours*
- *Leucovorin 400 mg /m^2 IV bolus*
- *Oxaliplatin 85 mg/m^2 IV over 2 hours*

Week 7:

- *Talimogene laherparepvec up to 4 mL of $1x10^7$ PFU/mL Or $1x10^8$ PFU/mL based on assigned dose level*
- *5-Fluorouracil (5-FU) 400 mg / m^2 IV bolus followed by 5-Fluorouracil (5-FU) 2400 mg / m^2 continuous IV infusion over 46 hours*
- *Leucovorin 400 mg /m^2 IV bolus*
- *Oxaliplatin 85 mg/m^2 IV over 2 hours*

Weeks 9 / 10:

- *Radiation 25 Gy over 5 fractions*

Weeks 12 / 13:

- *5-Fluorouracil (5-FU) 400 mg / m^2 IV bolus followed by 5-Fluorouracil (5-FU) 2400 mg / m^2 continuous IV infusion over 46 hours*
- *Leucovorin 400 mg /m^2 IV bolus*
- *Oxaliplatin 85 mg/m^2 IV over 2 hours*

Weeks 14 / 15:

- *5-Fluorouracil (5-FU) 400 mg / m^2 IV bolus followed by 5-Fluorouracil (5-FU) 2400 mg / m^2 continuous IV infusion over 46 hours*
- *Leucovorin 400 mg /m^2 IV bolus*
- *Oxaliplatin 85 mg/m^2 IV over 2 hours*

Weeks 16 / 17:

- *5-Fluorouracil (5-FU) 400 mg / m^2 IV bolus followed by 5-Fluorouracil (5-FU) 2400 mg / m^2 continuous IV infusion over 46 hours*
- *Leucovorin 400 mg /m^2 IV bolus*
- *Oxaliplatin 85 mg/m^2 IV over 2 hours*

Weeks 18 / 19:

- *5-Fluorouracil (5-FU) 400 mg / m^2 IV bolus followed by 5-Fluorouracil (5-FU) 2400 mg / m^2 continuous IV infusion over 46 hours*
- *Leucovorin 400 mg /m^2 IV bolus*
- *Oxaliplatin 85 mg/m^2 IV over 2 hours*

Dose Escalation Schedule				
Dose Level	**Dose**			
	Talimogene laherparepvec (PFU/ml)	**Capecitabine (mg/m^2 po bid on days of radiation)**	**Radiation (gray)**	**Comments**
Level 1	$1x10^6$, $1x10^7$, $1x10^7$,$1x10^7$	825	50.4 in 28 fractions	Completed prior to protocol amendment 1/23/21
Level 1 (amended)	$1x\ 10^6$, $1x\ 10^7$, $1x\ 10^7$,$1x\ 10^7$	N/A	25 Gray in 5 fractions	To be implemented if DLTs noted with DL 2
Level 2 (amended)	$1x10^6$, $1x10^8$, $1x10^8$,$1x10^8$	NA	25 in 5 fractions	
PFU = Plaque forming units; NA = Not applicable				

Talimogene laherparepvec will be administered via endoscopy by a qualified physician for a total of 4 doses as before but at the following amended time points: a) week 1 prior to initiation of FOLFOX chemotherapy b) weeks 3, 5 and 7 during FOLFOX chemotherapy

5.1.1 Talimogene laherparepvec

5.1.1.1. Talimogene laherparepvec dose and schedule

Please refer to section 8.1

5.1.1.2. Instructions for talimogene laherparepvec injection site care:

Care for injection site

IMPORTANT

- Reactions at or near the area of the injection have been seen in people administered talimogene laherparepvec. Symptoms include bleeding, redness, swelling and inflammation at the injection site. Skin infections 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, such as those mentioned above, at the injection site(s), you should contact the study doctor or his/her staff immediately.
- If there are signs that the surrounding skin is becoming irritated/red, please contact the study site. An absorbent pad may need to be applied.

Do Not:

- **Don't put salves or ointments on the injection site.**
- **Don't scratch or pick at the injection site**
- Avoid directly touching the area that has been injected with the study drug.

Infections: Tumor necrosis may be seen with the use of talimogene laherparepvec. The presence of necrotic or ulcerating lesions may pre-dispose the subject to local and/or systemic infections such as cellulitis, bacteremia, *etc.* Careful wound care and infection precautions are recommended if tumor necrosis results in open wounds.

In addition to monitoring patients for AEs related to talimogene laherparepvec, injection site will be evaluated directly during endoscopy at subsequent time points such as during pre-surgical evaluation and in those forgoing surgery needing endoscopic surveillance.

5.1.1.3.

Accidental Occupational Exposure: Accidental exposure may lead to transmission of talimogene laherparepvec and herpetic infection. Nurses and other study staff (*e.g.*, pharmacists) with open skin wounds should not come into direct contact with talimogene laherparepvec. HCP who are immunocompromised or pregnant should not prepare or administer talimogene laherparepvec. All personnel handling the virus or material contaminated with talimogene laherparepvec must observe safety precautions (e.g., wear a laboratory coat, safety glasses and gloves).

- In the event of an accidental occupational exposure through a splash to the eyes or mucous membranes, flush with clean water for at least 15 minutes. In the event of exposure to broken skin or needle stick, clean the site thoroughly with soap and water or a virucidal disinfectant such as 1% sodium hypochlorite or Virkon®.

Exposure of Non-treated Individuals to talimogene laherparepvec: As there is a potential risk for exposure of talimogene laherparepvec from subjects to anyone in direct contact with the subject, persons with open skin lesions or who are immunosuppressed, pregnant women

and newborns should avoid direct contact with the injected lesions, dressings or body fluids of the treated patients.

- In the event of a secondary exposure (*e.g.*, leakage through occlusive dressing to subject or contacts) to talimogene laherparepvec, clean the site thoroughly with soap and water or a virucidal disinfectant such as 1% sodium hypochlorite or Virkon®.

Persons should seek a healthcare provider for signs of systemic (fever, aches, nausea, and malaise) or local (fever, pain, redness and swelling) infection. Talimogene laherparepvec is sensitive to acyclovir which may be administered, if clinically indicated.

Accidental Spills: Spills should be treated with a virucidal agent. All disposable materials contaminated with talimogene laherparepvec must be destroyed and disposed of in compliance with local institutional guidelines.

5.1.2 *Other Agent(s)*

5.1.2.1 5-Fluorouracil

Patients will receive FOLFOX chemotherapy before and after radiation and after surgery per treating physician's discretion

5-FU is commercially available as a 50 mg/mL solution for injection in 10 mL, 20 mL, 50 mL and 100 mL vials. Inspect for precipitate; if found, agitate or gently heat in water bath. Bolus injections are prepared using undiluted drug. 46 hour infusion of 5-FU should be prepared for administration via ambulatory infusion pump according to the institution's standards. These solutions may be prepared in D5W or 0.9% NaCl. 5-FU should not be mixed in the same solution with most parenteral antiemetics.

Intact vials should be stored at room temperature and protected from light. Slight yellow discolor does not usually indicate decomposition. Stability in ambulatory pumps varies according to the pump, manufacturer of drug, concentration and diluent. Please refer to appropriate reference sources for additional information.

In this study, 5-FU is administered as a 400 mg/m2 IV bolus followed by 2400 mg/m2 by IV infusion over 46 hours starting immediately after the bolus.

5.1.2.2 Oxaliplatin

Patients will receive FOLFOX chemotherapy before and after radiation and after surgery per treating physician's discretion

Oxaliplatin is commercially available as an aqueous solution in vials containing 50 mg and 100 mg at a concentration of 5 mg/mL. The vials do not contain any preservative and they are intended for single use.

Intact vials should be stored at room temperature. Solutions diluted in D5W are stable for 6 hours at room temperature or 24 hours under refrigeration.

The calculated dose of oxaliplatin (85 mg/m^2 in this protocol) should be diluted for infusion with 250 mL to 500 mL D5W. Oxaliplatin should not be diluted with a sodium chloride solution. Needles, syringes, catheters or IV administration sets containing aluminum should not be used with oxaliplatin. As with other platinum compounds, contact with aluminum may result in a black precipitate.

Oxaliplatin will be administered by intravenous infusion over 2 hours. Infusion time may be prolonged (up to 6 hours) in patients experiencing pharyngolaryngeal dysesthesia or mild grade 1delayed hypersensitivity reactions. Oxaliplatin is unstable in the presence of chloride or alkaline solutions. Do NOT mix or administer oxaliplatin with saline or other chloride-containing solutions. Do NOT administer other drugs or solutions in the same infusion line. Flush IV lines/catheters with Dextrose 5% in Water both before and after oxaliplatin administration.

5.1.3 Other Modality(ies) or Procedures

5.1.3.1 Radiation Therapy

Radiation Therapy Schema:
The target dose to the pelvic PTV is 25 Gy with 5 Gy in 5 fractions during one week. The boost volume is included. An extra boost of 2 Gy x 2 – 3 is also possible to deliver in certain circumstances.

Target volumes

Boost GTV

Gross tumor volume (GTV) is the visible primary tumor and visible pathological lymph nodes.

CTV boost

GTV boost plus a margin of 2 cm within the same anatomical compartment as the tumor is in, for the dose from 45 to 50.4 Gy, also around radiologically engaged lymph nodes! If the tumor is entirely within mesorectum with no threatened MRF, the 2 cm extension for uncertainties in tumor spread does not need to go outside the fascia. The margin of 2 cm will thus chiefly be

added cranially and caudally. If the tumor e.g. grows into the sacral bone or the urinary bladder, the 2 cm margin does apply within those organs.

GTV boost plus a margin of 1 cm within the same anatomical compartment if an additional boost is given above 50.4 (or 50.0) or 25 Gy.

Pelvic CTV

1. The primary tumor

2. Primary lymph nodes in the bowel wall and within mesorectum. Mesorectum is composed of the surrounding fat around the bowel and extends dorsally towards sacrum. Distally, only lymph nodes or tumor deposits up to 4 cm are included. For tumors in lower rectum this means that the entire mesorectum down to the pelvic floor is included whereas in tumors high up in rectum, the most distal part of mesorectum is not included. The reason for this is to diminish radiation towards the sphincters.

3. The closest secondary lymph node stations consisting of presacral nodes and nodes along the rectal superior artery. These lymph nodes are partly overlapping with the primary mesorectal lymph nodes and they are important for all tumors within the rectum. Since local recurrences are very unusual above S1 – S2, lymph nodes above this level should not be included unless there are signs of pathological lymph nodes presacrally. If this is the case, the cranial limit of CTV should be at least 1 cm above the most cranial pathological lymph node.

4. The lateral lymph node stations along the medial rectal and obturator arteries until they reach the level of the obturator canal should be included if the primary tumor is below the peritoneal reflection or up to about 8 to 10 cm from the anal verge. In higher tumors, these nodes are rarely involved.

5. The lateral lymph node stations also include lymph nodes along the internal iliac artery up to the bifurcation from the external iliac artery. The cranial border for the CTV is in most cases just below the bifurcation of the internal and external iliac arteries. In most patients this is at the level of S1 – S2. In certain individuals, the bifurcation can be above L5 – S1. In these instances the cranial CTV border is at the level of S1-S2, unless lymph nodes along the internal iliac artery is seen. Then a margin of at least 1 cm above the most cranial lymph nodes must be drawn.

6. Inguinal lymph nodes are included in CTV only if the tumor grows into the anal canal and distal to the dentate line or if it grows into the distal part of vagina.

7. The entire ischio-rectal fossa, the anal canal and peritoneum is included in pelvic CTV only if the tumor grows into the levators or down into the anal canal. In these instances, rectal excision is always required.

8. Lymph nodes along the external iliac artery are included if the tumor grows into anterior organs like the prostate, urinary bladder, cervix, vagina or uterus to such an extent that the external nodes are at risk for metastases. Therefore, napping or minimal overgrowth dorsally is not sufficient.

PTV

The above description relates to the CTV. A PTV should normally be defined and includes CTV and internal target volume (ITV) and a margin necessary for the setup. These margins are depending upon several factors that are related to the equipment at the radiotherapy center.

Treatment verification

Treatment verification should be performed according to institutional guidelines. Acceptable deviations should be in line with the chosen CTV-PTV margin.

5.1.4 Investigational Imaging Agent Administration

N/A

5.2 Definition of Dose-Limiting Toxicity

Dose limiting toxicities (DLTs) will be captured until completion of FOLFOX chemotherapy (weeks 18/19) and will be graded according to the CTCAE ver 5. DLTs will be defined as clinically significant grade 3 or 4 toxicities possibly or probably related to study treatment. The following AEs will not be considered DLTs:

- any grade of alopecia,
- grade 3 arthralgia or myalgia,
- brief (< 1 week) grade 3 fatigue,
- grade 3 fever
- grade 3 diarrhea or vomiting responding to supportive care.
- grade 3 radiation dermatitis

All patients who have received at least one dose of the study regimen are evaluable for toxicities; for dose escalation decisions, patients should have completed ≥ 80% of the planned chemotherapy and radiation doses unless the reason for discontinuation is an AE that qualifies for DLT.

AEs that are considered "Dose Limiting" for talimogene laherparepvec

1) Herpetic events that should be considered DLTs:
   - Serious herpetic events such as herpetic encephalitis, encephalomyelitis or disseminated herpetic infection

- Any herpetic events confirmed due to talimogene laherparepvec that require treatment with acyclovir or similar anti-viral agent. Talimogene laherparepvec treatment should be held if systemic acyclovir or other anti-viral is indicated. If ongoing anti-viral treatment is required, talimogene laherparepvec treatment should be permanently discontinued

* Herpetic events due to wild-type HSV-1 or wild-type HSV-2 which require acyclovir and are not due to talimogene laherparepvec (as confirmed by PCR testing) should not be considered as DLTs caused by talimogene laherparepvec.

2) DLT will also be defined as any of the following talimogene laherparepvec-related toxicity:
   - Grade 2 or greater immune-mediated AEs.
   - Grade 2 or greater allergic reactions.
   - Any grade plasmacytoma
   - Any other grade 3 or greater hematologic or non-hematologic toxicity, with the exceptions of:
     - any grade of alopecia,
     - grade 3 arthralgia or myalgia,
     - brief (< 1 week) grade 3 fatigue,
     - grade 3 fever,
     - grade 3 diarrhea or vomiting responding to supportive case.

For other study treatments, DLT will be defined as clinically significant (ie excluding any grade alopecia, grade 3 arthralgia or myalgia, < 1 week grade 3 fatigue, grade 3 diarrhea, nausea, vomiting responding to supportive care), grade 3 or 4 toxicities possibly or probably related to study treatment or AEs.

Management and dose modifications associated with the above adverse events are outlined in Section 6.

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined above.

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.

1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level	This is generally the maximum tolerated dose, MTD. At least 6 patients must be entered at the MTD.

5.3 **Dose Expansion Cohorts:**

A total of 15 patients will be treated at the MTD (including the 6 from dose expansion) to assess safety and feasibility of this dose level. The MTD will be deemed to be recommended phase II dose (RP2D) if ≥ 80% of the patients are able to receive ≥ 80% of the planned treatment doses. If ≥ 1/3 of all patients at this dose experience DLTs, enrollment will be stopped and the Principal Investigator will discuss with all study investigators and with CTEP whether further addition of patients is needed to re-assess the RP2D. Monitoring of all safety and toxicity data is done by the Principal Investigator and the Corresponding Organization on a real-time basis as data are entered into Medidata Rave using the Web Reporting Module.

5.4 **General Concomitant Medication and Supportive Care Guidelines**

5.4.1 Talimogene laherparepvec is sensitive to acyclovir and other antiherpetic viral drugs, and would be rendered ineffective. Thus, if systemic anti-herpetic medication is indicated, talimogene laherparepvec should be discontinued.

5.4.2 Where to locate information:

- For “Instructions for talimogene laherparepvec Injection Site Care”, refer to Section 5.1.1.2
- For “Information Related to Exposure to talimogene laherparepvec”, refer to 5.1.1.3, Appendices C1, C2
- For Information Sheet for Patient, Close Contacts and Non-study HCP, please refer to Appendix C. This Information should be provided to the care giver, family members, and close contacts of patients receiving talimogene laherparepvec on this trial

5.5 **Duration of Therapy**

In the absence of treatment delays due to adverse event(s), treatment may continue for *the*

duration of the therapy per protocol or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s) Please refer to section 6 Treatment Modification Guidelines
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

5.6 Duration of Follow Up

Patients will be followed for 30 days after removal from study or until death, whichever occurs first. Patients who have undergone curative resection will be monitored for a minimum of 2 years (and up to 5 years) for disease recurrence. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Talimogene Laherparepvec Dose Delay and Treatment Discontinuation Guidelines

AEs that are considered "Dose Limiting" for talimogene laherparepvec Treatment Modification Guidelines

1) Herpetic events that should be considered DLTs:
    a. Serious herpetic events such as herpetic encephalitis, encephalomyelitis or disseminated herpetic infection
    b. Any herpetic events confirmed due to talimogene laherparepvec that require treatment with acyclovir or similar anti-viral agent. Talimogene laherparepvec treatment should be held if systemic acyclovir or other anti-viral is indicated. If ongoing anti-viral treatment is required, talimogene laherparepvec treatment should be permanently discontinued

    *Herpetic events due to wild-type HSV-1 or wild-type HSV-2 which require acyclovir and are not due to talimogene laherparepvec (as confirmed by PCR testing) should not be considered as DLTs caused by talimogene laherparepvec.
2) A DLT will also be defined as any of the following talimogene laherparepvec-related toxicity
    - Grade 2 or greater immune-mediated AEs.
    - Grade 2 or greater allergic reactions.
    - Any grade plasmacytoma
    - Any other grade 3 or greater hematologic or non-hematologic toxicity, with the exceptions of:
        - any grade of alopecia,
        - grade 3 arthralgia or myalgia,
        - brief (< 1 week) grade 3 fatigue,
        - grade 3 fever,
        - grade 3 diarrhea or vomiting responding to supportive care.

Dose Reductions/delay:

- Dose reductions with regards to changes in the concentrations of talimogene laherparepvec are not permitted. However, patients may require a reduction in the volume injected due to a disease response (defined in dosing section) or due to local toxicity at the injection site.
- If talimogene laherparepvec treatment was delayed due to AEs or other reasons by >1 week, that dose will be deemed to have been missed and the subject will proceed to the next scheduled treatment visit.
- If DLTs occur, talimogene laherparepvec administration should be delayed until the DLT has resolved to at least CTCAE version 5.0 Grade 1. (AEs less than DLT may also require talimogene laherparepvec dose delay. See instructions in Table below)
- If talimogene laherparepvec dosing is delayed by more than 4 weeks (approximately 6 weeks from the previous dose) due to treatment related AEs, talimogene laherparepvec should be permanently discontinued.
- If talimogene laherparepvec dosing is delayed by more than 4 weeks (approximately 6 weeks from the previous dose) for reasons other than treatment-related toxicity, the case

must be reviewed by the sponsor of the study (CTEP) to determine if the subject can resume talimogene laherparepvec therapy.

Treatment delays and discontinuation due to Specific AEs		
Condition	**Grade**	**talimogene laherparepvec modification**
• Injection site reactions		Volume of talimogene laherparepvec injection may be adjusted and should be held based on the degree of local toxicities
• Active herpetic cutaneous or mucosal lesions, herpes labialis, or active dermatosis in the region of the injected tumor (s)		Mild: continue talimogene laherparepvec; If requiring systemic acyclovir or similar anti-viral agents: Hold talimogene laherparepvec.
• Serious herpetic events such as herpetic encephalitis, encephalomyelitis or disseminated herpetic infection	Any grade	Discontinue talimogene laherparepvec
• Any condition requiring corticosteroid dosing of >10 mg prednisone daily (or equivalent) and/or other immunosuppressive medication for related toxicities	N/A	Hold talimogene laherparepvec dosing until corticosteroid dose has decreased to <10 mg prednisone daily (or equivalent) and the other immunosuppressive medication has been stopped.
• Plasmacytoma	Any grade	Permanently discontinue talimogene laherparepvec
• Immune-mediated AEs (These may include pauci-immune glomerulonephritis, vasculitis, and pneumonitis, but may involve any organ system)	Grade 2 or greater	Hold talimogene laherparepvec (with the exception of vitiligo). If delay is > 4 weeks, discontinue talimogene laherparepvec
• Allergic reactions, or urticaria	Grade 2 or greater	Hold talimogene laherparepvec. If delay is > 4 weeks, permanently discontinue talimogene laherparepvec

• Other talimogene laherparepvec related grade 3+ AEs or intolerable grade 2 AEs (Except brief grade 3 fever, fatigue, pain, or nausea/vomiting responding to supportive care)		Hold talimogene laherparepvec until AE is grade 0-1. • If delay is > 4 weeks, discontinue talimogene laherparepvec • If the AE was grade 4, decision to resume talimogene laherparepvec upon recovery should be reviewed with the sponsor (CTEP)

6.2 **Other Agent(s)**

Dose modification guidelines for talimogene laherparepvec are listed in Section 6.1.

Event Name	**Oxaliplatin Neuropathy**		
	Duration of Toxicity		
Grade of Event	**1-7 days**	**>7 days**	**Persistent between cycles**
Grade 1 Paresthesias/dysesthesias[b] that do not interfere with function	No change in dose	No change in dose	No change
Grade 2 Paresthesias/dysesthesias[b] interfering with function, but not activities of daily living (ADL)	No change in dose	No change in dose	Decrease by 1 dose level
Grade 3 Paresthesias/dysesthesias[b] with pain or with functional impairment that also interfere with ADL	No change	Decrease by 1 dose level	Stop oxaliplatin
Grade 4 Persistent paresthesias/dysesthesias that are disabling or life-threatening	Stop oxaliplatin	Stop oxaliplatin	Stop oxaliplatin
Laryngopharyngeal dysesthesia	↑ duration of next infusion to 6 hours[c]		
a Not resolved by the beginning of the next cycle.			

b May be cold induced.

Event Name	**Oxaliplatin hypersensitivity**
Grade of Event	**Management/Next Dose for Oxaliplatin**
≤ Grade 1	Premedications with antihistamines, steroids and slow rate of oxaliplatin by half with future doses
Grade 2	Premedications with antihistamines, steroids and slow rate of oxaliplatin by half with future doses or discontinue oxaliplatin per discretion of treating physician
Grade 3	Discontinue oxaliplatin
Grade 4	Discontinue oxaliplatin
*Patients requiring a delay of >2 weeks should go off protocol therapy.	

Event Name	**Hand Foot Syndrome**	
Grade of Event	**Management/Next Dose for Oxaliplatin**	**Management/Next Dose for 5-FU**
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Grade 3	Hold all treatment until recovery ≤ grade 1 but may continue radiation if deemed safe by investigators; No change in dose	Hold all treatment until recovery ≤ grade 1 but may continue radiation if deemed safe by investigators; No change in dose
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.		

Event Name	**Vomiting**	
Grade of Event	**Management/Next Dose for *Oxaliplatin***	**Management/Next Dose for *5-FU***
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**

Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.		
Recommended management: ondansetron 4-8 mg ODT or by mouth every 6-8 hours and / or prochlorperazine 5-10 mg po every 4-6 hours or other anti-emetics per treating physician		

Event Name	**Diarrhea**	
Grade of Event	**Management/Next Dose for Oxaliplatin**	**Management/Next Dose for 5-FU**
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Recurrent / persistent grade 2	Decrease by 1 dose level	Decrease by 1 dose level
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.		
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.		

Event Name	**Neutropenia**	
Grade of Event	**Management/Next Dose for *Oxaliplatin***	**Management/Next Dose for *5-FU***
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level; consider growth factor with next cycle	Hold until ≤ Grade 1. Resume at same dose level; consider growth factor with next cycle.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated; consider growth factor with next cycle especially if dose reduction not done.	Hold* until < Grade 2. Resume at one dose level lower, if indicated; consider growth factor with next cycle especially if dose reduction not done.
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.		
Consider GM-CSF per recommended doses		

Event Name	**Thrombocytopenia**

Grade of Event	Management/Next Dose for *[Agent Name]*	Management/Next Dose for *[Agent Name]*
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Recurrent Grade 2	Hold until ≤ Grade 1. Decrease by one dose level	Hold until ≤ Grade 1. Decrease by one dose level
Grade 3	Hold* until < Grade 2. Resume at one dose level lower	Hold* until < Grade 2. Resume at one dose level lower
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.		

Event Name	Mucositis	
Grade of Event	**Oxaliplatin**	**5-FU**
≤ Grade 1 or grade 2 but tolerable to patient	*No change in dose*	*No change in dose*
Grade 2 but intolerable to patient	No change in dose	Decrease by one dose level
Grade 3	Hold all treatment until < Grade 2. No change in dose	Hold all treatment until < Grade 2. Decrease by one dose level
Grade 4	Discontinue treatment	Discontinue treatment
* Patients requiring a delay of >2 weeks should go off protocol therapy.		
Recommended Management: Oral hygiene, topical mucosal coating agents such as diphenhydramine, compounded mixtures of topical anaesthetics		

Event Name	Fatigue	
Grade of Event	**Oxaliplatin**	**5-FU**
≤ Grade 1 or grade 2 but tolerable to patient	*No change in dose*	*No change in dose*
Grade 2 but intolerable to patient	Decrease by one dose level	Decrease by one dose level
Grade 3	Hold all treatment until < Grade 2. Decrease by one dose level	Hold all treatment until < Grade 2. Decrease by one dose level
Grade 4	Discontinue treatment	Discontinue treatment
* Patients requiring a delay of >2 weeks should go off protocol therapy.		
Recommended Management: Physical exercise / therapy, light exposure, evaluate for contributing factors including medications, anemia, poor sleep hygiene		

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7 .1) and the characteristics of an observed AE (Sections 7.2 **and 7.3**) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) in addition to routine reporting

7.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset of AEs, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The SPEER is a list of events that are protocol-specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm for further clarification.

The CAEPR may not provide frequency data; if not, refer to the Investigator's Brochure for this information.

NOTE: The highest grade currently reported is noted in parentheses next to the AE in the SPEER. Report **ONLY** AEs higher than this grade expeditiously. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

7.1.1 CAEPRs for CTEP IND Agent(s)

7.1.1.1 CAEPR for talimogene laherparepvec

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Talimogene Laherparepvec(NSC 785349)

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Talimogene laherparepvec (T-VEC, IMLYGIC, NSC 785349)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 517 patients.* Below is the CAEPR for Talimogene

laherparepvec (T-VEC, IMLYGIC).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.1, August 22, 2017[1]

Adverse Events with Possible Relationship to Talimogene laherparepvec (T-VEC, IMLYGIC) (CTCAE 5.0 Term) [n= 517]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Chills			***Chills (Gr 2)***
Fatigue			***Fatigue (Gr 2)***
Fever			***Fever (Gr 2)***
Flu like symptoms			***Flu like symptoms (Gr 2)***
Injection site reaction[2]			***Injection site reaction[2] (Gr 2)***
	Pain[3]		***Pain[3] (Gr 2)***
IMMUNE SYSTEM DISORDERS			
		Autoimmune disorder[4]	
INFECTIONS AND INFESTATIONS			
	Infections and infestations - Other (herpetic keratitis)		
	Infections and infestations - Other (oral herpes)		
	Skin infection[5]		***Skin infection[5] (Gr 2)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Wound complication[6]		
INVESTIGATIONS			
	Weight loss		***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Dehydration		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		***Pain in extremity (Gr 2)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			

Adverse Events with Possible Relationship to Talimogene laherparepvec (T-VEC, IMLYGIC) (CTCAE 5.0 Term) [n= 517]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (plasmacytoma at the injection sites)	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pharyngolaryngeal pain		***Pharyngolaryngeal pain (Gr 2)***
		Respiratory, thoracic and mediastinal disorders - Other (obstructive airway disorder)[7]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Pruritus		
	Rash[8]		
	Skin and subcutaneous tissue disorders - Other (dermatitis)		
	Skin and subcutaneous tissue disorders - Other (vitiligo)[4]		
VASCULAR DISORDERS			
	Flushing		
	Thromboembolic event (venous)		
		Vascular disorders - Other (carotid artery blowout syndrome)[9]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Injection site reactions may include redness, swelling, and bleeding.

[3]Pain can occur in the tumor, injection sites and nodal draining (axilla and groin etc) lymph nodes.

[4]Several events which are autoimmune-mediated, such as acute kidney injury (acute renal failure), glomerulonephritis (nephritis), worsening of psoriasis, pneumonitis, vasculitis, and vitiligo (areas of skin with loss of color) have been observed in clinical trials of talimogene laherparepvec.

[5]Skin infection (cellulitis) can be complicated with local and systemic infection, tissue necrosis, and ulceration, or wound complications.

[6]Wound complication may occur at the injection site and may include wound infection and poor healing.

[7]Obstructive airway disorder has occurred in one patient with Head and Neck Squamous cell carcinoma (HNSCC) with a suproventricular mass who developed acute respiratory distress requiring a trachetomy 13 days after the second dose of T-VEC. Imaging showed a mass in the larynx and adjacent lymph nodes on the contralateral side.

[8]Rash may include rash maculo-papular and erythematous rash.

[9]Carotid artery blowout syndrome was observed in a HNSCC patient treated with T-VEC in combination with anti-PD-1 who had been previously treated with localized (neck) radiation and lymph node dissection.

Adverse events reported on talimogene laherparepvec (T-VEC, IMLYGIC) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that talimogene laherparepvec (T-VEC, IMLYGIC) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
CARDIAC DISORDERS - Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus
GASTROINTESTINAL DISORDERS - Ascites; Dry mouth; Dysphagia; Gastrointestinal disorders - Other (odynophagia); Mucositis oral
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Malaise
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (oral candidiasis)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Dermatitis radiation; Fracture
INVESTIGATIONS - Neutrophil count decreased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hypokalemia
NERVOUS SYSTEM DISORDERS - Cognitive disturbance; Dysgeusia
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Insomnia
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Pneumonitis[4]

Note: Talimogene laherparepvec (T-VEC, IMLYGIC) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Note: In animal models talimogene laherparepvec has demonstrated several potential risks as detailed below:

1) Talimogene laherparepvec has **not** been tested in severely immune compromised patients. In animal models, injection of talimogene laherparepvec in immune-deficient mice resulted in disseminated infection.
2) Transmission of talimogene laherparepvec to health care professionals and personnel in close contact is possible.
3) Latent infection of talimogene laherparepvec in the neurological system has been observed in mice at high dose of T-VEC, although the clinical implication in human patients is not clear.

7.1.2 Adverse Event List(s) for Commercial Agent(s)

7.1.2.1 **5-FU:**

Gastrointestinal Disorders: Diarrhea, nausea, stomatitis, vomiting, abdominal pain, constipation, dyspepsia, elevated liver function tests

Skin and Subcutaneous Tissue Disorders: Hand-foot syndrome, alopecia, rash, erythema, skin discoloration

General Disorders: Fatigue, Pyrexia, asthenia, lethargy, anorexia

Nervous System Disorders: Dizziness, headache, dysgeusia

Blood and Lymphatic Disorders: Anemia, thrombocytopenia and neutropenia

7.1.2.2 **Oxaliplatin:**

Gastrointestinal Disorders: Diarrhea, nausea, stomatitis, vomiting, constipation, dyspepsia, elevated liver function tests

Cardiovascular Disorders: Hypotension

Skin and Subcutaneous Tissue Disorders: Hand-foot syndrome, alopecia, rash, erythema, skin discoloration

General Disorders: Fatigue, Pyrexia, asthenia, lethargy, anorexia

Nervous System Disorders: Dizziness, headache, dysgeusia, paresthesias, pharyngo-laryngeal dysthesias

Blood and Lymphatic Disorders: Anemia, thrombocytopenia and neutropenia

Hypersensitivity and injection site reactions

For further details regarding adverse events, please refer to the package insert for each agent

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

- Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.5.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions". Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological

changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.3.4 **Additional talimogene laherparepvec specific Reporting Guidelines –**

Reporting is required for: (1) suspected herpetic events in treated patients; (2) suspected herpetic events in at-risk HCPs with direct or indirect exposure to talimogene laherparepvec; and 3) suspected herpetic events in the treated patient's close contacts. The mechanism, timing, and follow-up procedures are summarized in the table below and described in Section 7.3.4.1 (for treated patients) and 7.3.4.2 (HCPs and close contacts).

Accidental Exposure and Herpetic Event Reporting Requirement Summary

Exposed Person	**Reporter**	**Timeframe for Reporting to Amgen**	**Report Mechanism**	**Timing of Swab Collection**	**qPCR Testing Required?**	**Responsible Party for Lesion Swabbing**	**qPCR Test Result Distribution ***
Treated Patients with suspected herpetic lesions	Investigator	Within 24 hours of Investigator awareness	Contact **Amgen** at 1-855-IMLYGIC (1-855-465-9442) **AND** Report to **CTEP** through **CTEP-AERS**	Collect swabs from suspected lesions ideally within 3 days of appearance of symptoms	Yes, if consent obtained	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 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 (e.g., caregiver, spouse, child) **with suspected herpetic lesions**	Close Contact's Personal Physician or Close Contact	**Within 24 hours** of Reporter awareness	Contact **Amgen** at 1-855-IMLYGIC (1-855-465-9442) to report event	Collect swabs from suspected lesions within 3 days of appearance of symptoms	Yes, if consent obtained	Close Contact's Personal Physician	Close Contact's Personal Physician and Amgen

Accidental talimogene laherparepvec exposure and suspected infection in study patients receiving talimogene laherparepvec:

If the patient receiving talimogene laherparepvec on study has developed signs or symptoms of herpetic infection, the event must be reported to Amgen AND CTEP-AERS and patient should be followed up by the study team for viral assays:

1) Report to **CTEP-AERS** as SAE.
2) Notify **Amgen immediately (within 24 hours)** upon knowledge of suspected infection). Contact the **Amgen Call Center at 1-855-IMLYGIC (1-855-465-9442).**

- Patient should be seen by the study physician. The herpetic lesions should be tested for DNA specific to talimogene laherparepvec. **This testing must occur within three days of the appearance of the symptoms**:
- Swabs of cold sore, vesicles or any other lesions suspected to be herpetic in origin should be obtained.
- **Amgen will provide the qPCR test manual for sample collection and shipment to Viracor**
- qPCR or other testing for wild type HSV-1 is not required. A commercially available test should be ordered if the investigator believes it is clinically indicated.

Accidental Exposure of Health Care Provider (HCP) to talimogene laherparepvec without herpetic symptoms and signs:

If the HCP is suspected to have been exposed to talimogene laherparepvec (direct exposure, e.g. needle sticks, splash) without signs or symptoms of herpetic infection, the event must be reported to Amgen.

1) Report to Amgen by calling **Amgen Call Center at 1-855-IMLYGIC (1-855-465-9442).**

Accidental Exposure and Secondary Transmission of talimogene laherparepvec to **Close Contacts or Health Care Provider (HCP) with** symptoms/signs of herpetic infection:

If a close contact or HCP is suspected to have been exposed to talimogene laherparepvec (with signs or symptoms of herpetic infection, the event must be reported to Amgen. Amgen will provide instructions regarding follow up with physicians and talimogene laherparepvec testing.

2) **Report to Amgen** immediately **(within 24 hours)** as symptoms or signs are observed. Contact the **Amgen Call Center at 1-855-IMLYGIC (1-855-465-9442).**

- Amgen will provide close contacts/HPC with instructions to see physicians for management and evaluation of talimogene laherparepvec DNA. **This testing must occur within three days of the appearance of the symptoms:**
- The physicians of HCP or Close Contacts will be responsible for obtaining the swab of herpetic lesions and submitting it to talimogene laherparepvec testing,

per instructions from Amgen.

3) Also refer to instructions in the Information Sheet for Close Contacts.

***NOTE**: Close contacts in regions where talimogene laherparepvec is commercially available should contact their HCP to evaluate the lesions. In the US, suspected herpetic lesions should be reported to Amgen as instructed above. Close contacts have the option of follow-up testing for further characterization of the infection. This test is likely to be more reliable if it can be performed within the first three days of symptoms appearing.

***NOTE**: Close contacts in regions where talimogene laherparepvec is not commercially available (e.g. Canada) may contact their HCP for evaluation and appropriate treatment. They should come to the study site for sample collections for qPCR testing for suspected herpetic lesions. This test is likely to be more reliable if it can be performed in the first three days of symptoms appearing.

7.3.5. Reporting requirements to NIH Office of Scientific Policy (OSP) and local Institutional Biosafety Committee (IBC)

Because talimogene laherparepvec (T-VEC) is a gene transfer agent, all protocols should follow the NIH Office of Scientific Policy (OSP) guidelines, including protocol submission, AE reporting and Annual Reports to OSP (http://osp.od.nih.gov/sites/default/files/resources/NIH_Guidelines_PRN_1-sided.pdf. **Compliance with the OSP requirements is the responsibility of the Principle and Participating Investigators**. In addition, all participating sites should follow the guidelines of local IBCs.

Investigators should review the OSP website (above) for complete instructions. Key (not all) OSP requirements are outlined below:

- Registration of the protocol with OSP (no less than 10 days before anticipated protocol activation) – to be done by Principle Investigator (see Section 7.3.5.1)
- Reporting of the initiation of the protocol (within 30 days of the first patient enrollment on the protocol) – by Principle Investigator (Section 7.3.5.2)
- Submission of IBC approval to OSP (within 30 days of first patient enrollment at the site) – by Participating Sites (Section 7.3.5.3)
- Annual reports to OSP - By Principle investigator or delegate (Section 7.3.5.4)
- IND safety reports to OSP - by Principle Investigator or delegate (Section 7.3.5.5)

7.3.5.1. **Registration of protocol with OSP**: This should occur *before* protocol activation. (Appendix M-I-A and M-I-B of the OSP guidelines http://osp.od.nih.gov/sites/default/files/NIH_Guidelines.html#_Toc446948493)

The **Principle Investigator** or coordinating site IBC should submit the following to OSP no less than 10 days before the anticipated protocol activation.

- The proposed protocol and Inform Consent Form (these documents does not have to be the final, IRB-approved version)

- Institutional Biosafety Committee (IBC)'s review or letter

Submission to OSP should be done preferably by e-mail to: HGTprotocols@mail.nih.gov; additional contact information is also available on the OSP website http://www.osp.od.nih.gov/about/contact-us/

An NIH OSP acknowledgement that the protocol registration process is complete will occur within the 10 working days prior to the anticipated date of enrollment. Final IBC approval may then be granted

7.3.5.2. **Reporting of Initiation of the Clinical Investigation** (Appendix M-I-C-1 Packet of OSP guidelines http://osp.od.nih.gov/sites/default/files/NIH_Guidelines.html#_Toc446948493):

The Principle Investigator of the protocol should submit the following documents to NIH OSP, no later than 30 working days after the first patient enrollment to the trial.

1) A cover letter with the following information: applicable NIH grant number(s), the FDA IND number, any modifications to the protocol as required by FDA, the date of the initiation of the trial.
2) A copy of the protocol approved by the local Institutional Biosafety Committee (IBC) and IRB;
3) A copy of the informed consent document (ICD) approved by the Institutional Review Board (IRB);
4) A copy of the final IBC approval from the clinical trial site,
5) A copy of the final IRB approval;

7.3.5.3. Requirement for **all Participating Institutions** (Appendix M-I-C-2 Packet of OSP guidelines http://osp.od.nih.gov/sites/default/files/NIH_Guidelines.html#_Toc446948493)

- For patient enrollment, all participating sites should obtain approval from the local IBC before patients can be enrolled at the site**.** Local IBC guidelines such as safety reporting requirements should also be followed.
- The following should be submitted to OSP within 30 days of the first patient enrollment at the site:
    1) IBC approval from the participating site;
    2) IRB approval (if CIRB is used, submit CIRB approval);
    3) IRB-approved informed consent document (ICD);

4) NIH grant number(s) if applicable.

7.3.5.4. **Annual Reports** (Appendix M-I-C-3 Annual Report http://osp.od.nih.gov/sites/default/files/NIH_Guidelines.html#_Toc446948493) – by Principle Investigator or delegate

Within 60 days after the one-year anniversary of the date on which the investigational new drug (IND) application went into effect, and after each subsequent anniversary until the trial is completed, the Principal Investigator (or delegate) shall submit the information set forth in (a), (b), and (c) (see Appendix M-I-C-3 in the link above), which shall include Clinical Trial Information, Progress Reports and Analysis, and Updated Protocol. When multiple studies are conducted under the single IND, the Principal Investigator (or delegate) may choose to submit a single annual report covering all studies, provided that each study is identified by its OSP protocol number.

7.3.5.5: Reporting of SAEs

Principle investigators (or delegate) should submit SAEs that are serious, unexpected and related (i.e. IND Safety Reports) to OSP at the same timeline as for FDA reporting.

In addition, SAEs or other AEs should be reported to local IBC per local IBC guidelines.

Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 7.4):

CTCAE SOC	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Attribution	Comments
	Diarrhea	≤ 3	< 7 days	Any	
	Vomiting	≤ 3	< 7 days	Any	
	Fatigue	≤ 3	< 7 days	Any	
	Radiation Dermatitis	≤ 3	< 7 days	Any	

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

7.5 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine AE reporting mechanisms outlined in this protocol i.e. the adverse event CRF in Rave. Pathology report may be uploaded when available but is not required.

7.6 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies in talimogene laherparepvec protocols should also be reported expeditiously via CTEP-AERS.

7.7 Surgical Complications

Surgical complications will be graded and reported using the Clavein Dindo classification as follows:

Grade I: Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions.
Allowed therapeutic regimens are: drugs as antiemetic, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.

Grade II: Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.

Grade III: Requiring surgical, endoscopic or radiological intervention

Grade III-a: Intervention not under general anesthesia

Grade III-b: Intervention under general anesthesia

Grade IV: Life-threatening complication (including CNS complications: brain hemorrhage, ischemic stroke, subarachnoid bleeding, but excluding transient ischemic attacks) requiring IC/ICU management.

Grade IV-a: Single organ dysfunction (including dialysis)

Grade IV-b: Multi-organ dysfunction

Grade V: Death of a patient

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8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.1.

8.1 CTEP IND Agent(s)

8.1.1 Talimogene laherparepvec(NSC 785349)

Other Names: talimogene laherparepvec, AMG 678; OncoVEX^{GM-CSF}, IMLYGIC™

Classification: Oncolytic immunotherapy

Product Description: talimogene laherparepvec is an oncolytic immunotherapy based on a modified herpes simplex virus type-1 (HSV-1). It selectively replicates and induces viral lysis of tumor cells resulting in an immune response specific to subjects' tumor.

8.1.2 **How Supplied:** Amgen supplies talimogene laherparepvec and the Pharmaceutical Management Branch distributes. There are two nominal vials concentrations:

- 1x **10^6 PFU/mL** packaged as 10 vials per box
- 1x **10^8 PFU/mL** Packaged as 20 vials per box

Both vials strengths contain 1 mL extractable volume (with approximately0.1 mL overfills volume) of talimogene laherparepvec solution consisting of disodium hydrogen phosphate dehydrate, sodium dihydrogen phosphate dehydrate, sodium chloride, sorbitol, myo-inositol and Water for Injection. T-vec is a sterile, semi-translucent to opaque suspension, practically free from particles, preservative

free frozen liquid packaged in a single-use 2 mL Crystal Zenith Resin vial. Each vial is sealed with a gray stopper (latex-free) and is Fluorotec-coated on the product side.

Current supplies of talimogene laherparepvec are provided as a preservative-free solution in a single-use vial without a clear copolyester plastic sleeve.

In early 2019, talimogene laherparepvec vials will change in appearance only. Supplies will be transitioned to single-use vials permanently inserted into a clear copolyester plastic sleeve. The product label will be found on the vial sleeve. Talimogene laherparepvec vial is compatible with the Closed System Transfer Device (CSTD), PhaSeal CSTD.

Preparation (1x 10^6 PFU/mL and 1x 10^8 PFU/mL):

Thawing process:

- Remove the number of frozen vials from the box that have been calculated for administration and immediately (within 90 seconds) return the remaining vials to the freezer**.** Care should be taken to avoid unintended thawing of vials that will not be used. The time the vials are removed from the freezer must be recorded. Thaw frozen vial(s) at room temperature, 15°C to 30°C (59°F to 86°F) until liquid (approximately 30 minutes). Do not expose vial(s) to higher temperatures. Protect vial(s) from light during the thaw process.
- Do not shake vial(s)
- Gently swirl vial(s) for completion of thaw
- Carefully check the vial(s) for cracks
- DO NOT re-freeze thawed vial(s)

After thawing:

- Gently swirl the vial(s) to ensure the contents are mixed to a homogeneous solution free of ice.
- Carefully check the vial(s) for damage (e.g., cracks). Dispose of damaged vial(s) according to the institutional policy and guidelines and notify PMB at pmbafterhours@mail.nih.gov.
- Draw required dose volume according to the tumor size injection volume (see below) into a syringe that is properly labeled.
- Protect from light until administration

Stability at 2°C to 8°C (36^0 F to 46^0 F)			
Thawed vial stability		Prepared syringe stability	
1 x 10^6 PFU/mL	**1 x 10^8 PFU/ mL**	**1x 10^6 PFU/mL**	**1x 10^8 PFU/ mL**
12 hours (inclusive of 4 hours maximum in the syringe)	48 hours (inclusive of 8 hours maximum in syringe)	4 hours	8 hours

Stability up to 27°C (80^0 F)			
Thawed vial stability		Prepared syringe stability	
1x 10^6 PFU/mL	**1x 10^8 PFU/ mL**	**1x 10^6 PFU/mL**	**1x 10^8 PFU/ mL**
4 hours (inclusive of 2 hours maximum in the syringe)	4 hours (inclusive of 4 hours maximum in the syringe)	2 hours	4 hours

Preparation (1x 10^7 PFU/mL: (dilution must be prepared in syringe)

- Thaw one vial of 1x **10^8 PFU/mL** as instructed above
- Use a 10 mL syringe with a 22-26G needle withdraw 1 mL talimogene laherparepvec
- Add 9 mL of 0.9% Sodium Chloride bringing volume to 10 mL
- Properly label syringe
- Protect from light until administration

1x10^7 PFU/mL (Stability in syringe)	
2°C - 8°C (36^0 F to 46^0 F)	**up to 27°C (80^0 F)**
8 hours (after dilution in 0.9% NaCl)	4 hours (after dilution in 0.9% NaCl)

Talimogene laherparepvec injection volume guideline: Lesions should be injected until either the maximum volume is reached or there are no further injectable lesions, whichever comes first. The total injection volume for each treatment visit should not exceed 4 mL for all injected lesions combined.

Tumor Size (longest dimension)	Injection Volume PER Lesion

> 5 cm	4mL
> 2.5 cm to 5cm	2 mL
> 1.5 cm to 2.5 cm	1 mL
> 0.5 cm to 1.5 cm	0.5 mL
≤ 0.5 cm	0.1 mL

Please replace the storage and stability as follow:

Storage: Talimogene laherparepvec intact vials are stable between -90^{0}C and -70^{0}C, protect from light. [Note: Frost-free, auto defrosts freezers must not be used since they cycle to warmer temperatures several times a day.]

Freezer Set Point	Acceptable Range
-80^{0}C	-90^0 C to - 70^0 C

Stability: Shelf-life surveillance of the intact vials is on-going.

If a storage temperature excursion is identified, promptly return talimogene laherparepvec to between -90^0 C and - 70^0 C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

NOTE: Upon receipt of the agent supplies, the site has **90 seconds** to verify the contents and place the agent supplies in the -80^{0}C (+/- 10^0 C) freezer once the inner shipping container lid is opened and the supply exposed to room temperature (See Appendices F & G).

Route of Administration: Intratumoral / intralesional injection

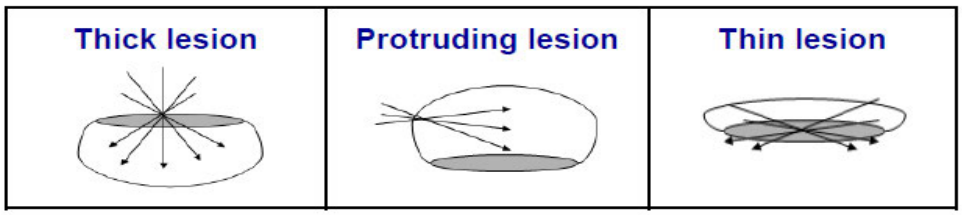
Method of Administration: talimogene laherparepvec is to be administered by intralesional injection into cutaneous, subcutaneous and nodal lesions with or without image ultrasound guidance. Talimogene laherparepvec must not be administered into visceral organ metastases.

Injection site may be pre-treated with a topical or a local anesthetic agent; however, a local anesthetic must not be injected directly into the lesion.

Intralesional injection guidance:

- A single point of injection is recommended; multiple insertion points may be used if the tumor is larger than the radial reach of the needle.

- Inject talimogene laherparepvec along multiple different tracks within the lesion in order to obtain as wide a dispersion as possible
- Distribute talimogene laherparepvec within the lesion through the insertion point using the radial reach of the needle in different directions to evenly distribute



- Avoid premature extraction of needle
- After dosing, the injection site should be swabbed with alcohol and pressure should be applied with gauze for several seconds after injection
- Cover the injection site with an absorbent pad and dry occlusive dressing

Special Handling: Talimogene laherparepvec is an attenuated version of HSV-1. Use protective equipment when preparing and administering this agent according to the institutional guidelines. In the event of an accidental occupational exposure through a splash to the eyes or mucous membranes, flush with clean water for at least 15 minutes. In the event of exposure to broken skin or needle stick, clean the site thoroughly with soap and water or a virucidal disinfectant such as 1% sodium hypochlorite or Virkon®.

In the event of a secondary exposure (e.g., leakage through occlusive dressing to subject or contacts) to talimogene laherparepvec, clean the site thoroughly with soap and water or a virucidal disinfectant. Seek healthcare provider for signs of systemic (fever, aches, nausea, and malaise) or local (fever, pain, redness and swelling) infection.

Patient Care Implications:

- Advise patients on the potential for secondary exposure, e.g., broken skin. Advise patients on careful wound care.
- Necrotic or ulcerating lesions may occur and may be predisposed to local and/or systemic infections such as cellulitis, bacteremia, etc. Advise patients on careful wound care. Infection precautions are recommended for tumor necrosis that results in open wounds.
- There is a potential risk for exposure of talimogene laherparepvec from patients to anyone in direct contact with the patient. Individual with open skin lesions and immunosuppressant should not come in contact with talimogene laherparepvec injection site or its protective dressing.
- An Information Sheet about talimogene laherparepvec and the risk of transmission and accidental exposure should be provided to patient's Health Care Providers and Close Contacts (see Appendix C)
-

Availability

Talimogene laherparepvec is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Talimogene laherparepvec is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.3 Agent Ordering and Agent Accountability

8.1.3.1 NCI-supplied agents may be requested by the responsible investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

SPECIAL INSTRUCTIONS:

Initial agent supplies may be requested only when subject enrollment onto the study is confirmed.
There will be NO next day delivery of Talimogene laherparepvec requests available. Sites must plan agent ordering and study subject treatment accordingly.
Agent order requests received on Monday, Tuesday, or Wednesday of the week, will be shipped on Tuesday, Wednesday and Thursday, respectively. Agent order requests received on Thursday or Friday of the week will be shipped on Monday of the following week. There will be no exceptions to this planned schedule. Sites should also consider planned Federal Government holidays when submitting agent requests and scheduling study subject treatment.

Talimogene laherparepvec will be shipped on dry ice. Only one strength of the agent will be in a single shipping container. You may receive multiple shipping containers for a single strength depending on the number vials being shipped. Upon receipt of the agent supplies, the site has 90 seconds to verify the contents and place the agent supplies in the -80^{0}C (+/- 10^0 C) freezer (see Appendix…) once the inner shipping container lid is opened and the supply exposed to room temperature. Record exposure time in the temperature exposure tracking log (see Appendices F & G). The log must be retained with your study records. If exposure time exceeds 90 seconds, quarantine the agent supplies in the -80^{0}C (+/- 10^0 C) freezer and call PMB immediately at 240-276-6575 for guidance.

8.1.3.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.3.3 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov

8.2 Commercial Agent(s)

8.2.1 5-fluorouracil (5-FU) & Leucovorin (LV)

5-FU

Product description: 5-FU is commercially available as a 50 mg/mL solution for injection in 10 mL, 20 mL, 50 mL and 100 mL vials. Intact vials should be stored at room temperature and protected from light. Slight yellow discolor does not usually indicate decomposition. Stability in ambulatory pumps varies according to the pump, manufacturer of drug, concentration and diluent.

Solution preparation: Inspect for precipitate; if found, agitate or gently heat in water bath.

Bolus injections are prepared using undiluted drug.
46 hour infusion of 5-FU should be prepared for administration via ambulatory infusion pump according to the institution's standards. These solutions may be prepared in D5W or 0.9% NaCl. 5-FU should not be mixed in the same solution with most parenteral anti-emetics.

Route of administration: In this study, 5-FU is administered as an IV bolus on day 1 on FOLFOX followed by IV infusion over 46 hours starting immediately after the bolus.

Agent Ordering: 5-FU is commercially available

Please refer to package insert for complete product information

Leucovorin (LV)
Product description: LV is commercially available as a 10 mg/mL in sterile, single use vials. Intact vials should be stored at 68 F – 77 F and protected from light.

Solution preparation: Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. Leucovorin for injection should be reconstituted with sterile water

Route of administration: In this study, LV is administered as an IV bolus on day 1. 5-Fluorouracil and leucovorin should be administered separately to avoid the formation of a precipitate.

Agent Ordering: LV is commercially available

Please refer to package insert for complete product information

8.2.2 Oxaliplatin

Product description: Oxaliplatin is commercially available as an aqueous solution in vials containing 50 mg and 100 mg at a concentration of 5 mg/mL. The vials do not contain any preservative and they are intended for single use. Intact vials should be stored at room temperature. Solutions diluted in D5W are stable for 6 hours at room temperature or 24 hours under refrigeration.

Solution preparation: The calculated dose of oxaliplatin should be diluted for infusion with 250 mL to 500 mL D5W. Oxaliplatin should not be diluted with a sodium chloride solution. Needles, syringes, catheters or IV administration sets containing aluminum should not be used with oxaliplatin. As with other platinum compounds, contact with aluminum may result in a black precipitate.

Route of administration: Oxaliplatin will be administered by intravenous infusion over 2 hours on day 1 of FOLFOX in this study. Infusion time may be prolonged (up to 6 hours) in patients

experiencing pharyngolaryngeal dysesthesia. Oxaliplatin is unstable in the presence of chloride or alkaline solutions. Do NOT mix or administer oxaliplatin with saline or other chloride-containing solutions. Do NOT administer other drugs or solutions in the same infusion line. Flush IV lines/catheters with Dextrose 5% in Water both before and after oxaliplatin administration.

Agent Ordering: Oxaliplatin is commercially available

Please refer to package insert for complete product information

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Collection of Specimens

Tissue should be collected, fixed in formalin for 12-24 hours and shipped to the ETCTN Biorepository in 70% Ethanol where it will be embedded as FFPE blocks on-site. Additional portions of this material will undergo extraction of nucleic acids for whole exome sequencing and RNA sequencing. In order to maintain consistent and reliable quality of the tissue specimens for these downstream analyses, the length of fixation time in formalin must be strictly controlled. For this reason, core biopsy samples will be collected in formalin and shipped overnight to the ETCTN Biorepository at Nationwide Children's Hospital. Specimen shipment kits will be provided. The ETCTN Biorepository will perform the embedding, cut slides and distribute them to the immunohistochemistry laboratory. The ETCTN Biorepository will also extract the nucleic acids from a separate portion of the FFPE material for shipment to the sequencing laboratory.

Biopsies and blood samples are obtained at the time points indicated in the Table below. Every effort should be made to obtain both pre-treatment and on-treatment tissue biopsies.

Two tissue cores will be collected and embedded in paraffin at the trial sites. The first or highest quality core will be used for the PD-L1 and TIL IHC assays. The second core will be used for whole exome sequencing and RNAseq. An additional 1-2 cores will be frozen in cryovials for flow cytometry. All tissue will be sent to the biorepository for storage and distributed to their respective labs upon completion of the study. FFPE cores may be stored at room temperature. For IHC assays, CIMAC labs generally request 10 fresh cut slides and do not need a full block. Discussions regarding the processing of NaHep blood tubes for flow cytometry have been deferred until a CIMAC lab has been chosen and the lab's needs have been identified.

Summary of specimen requirements:

Time Point	Specimen and Quantity	Send Specimens to:
Archival Specimens		
	• 2 FFPE tissue cores[1]	ETCTN Biorepository
Baseline		

	• 2 FFPE tissue cores[1] • 1-2 tissue cores snap-frozen[1] • 20 mL blood in green-top Na-Hep tube • 10 mL blood in cfDNA Streck tube	ETCTN Biorepository
	• 2 mL EDTA whole blood[2]	ETCTN Biorepository
Week 7		
	• 2 FFPE tissue cores[1] • 1-2 tissue cores snap-frozen[1] • 10 mL blood in cfDNA Streck tube	ETCTN Biorepository
	• 20 mL blood in green-top NaHep tube	ETCTN Biorepository
Week 30-35		
	• 2 FFPE tissue cores[1] • 1-2 tissue cores snap-frozen[1] • 10 mL blood in cfDNA Streck tube	ETCTN Biorepository
	• 20 mL blood in green-top NaHep tube	ETCTN Biorepository

[1]A copy of the radiology and operative reports from the tissue removal procedure must be sent with the tissue to the ETCTN Biorepository. When completed, upload the corresponding pathology reports to Rave.
[2] This may be collected at a later time point for patients already on-study.

9.2 Specimen Procurement Kits and Scheduling:

Specimen Shipping Kits

Kits for the collection and shipment of specimens to the ETCTN Biorepository can be ordered online via the **Kit Management system** (https://ricapps.nationwidechildrens.org/KitManagement). Sites will need to set up an account in the Kit Management system and select a specific clinical trial protocol to request a kit. Each user may order two kit types per protocol per day (daily max = 6 kits). Kits are shipped ground, so please allow 5-7 days for receipt. A complete list of kit contents for each kit type is located on the Kit Management system website.

Scheduling of Specimen Collections

Tumor tissue cores collected during biopsy procedures and fixed in the formalin must be shipped on the same day of collection. Tissue can be collected Monday through Wednesday, and shipped overnight (FedEx Priority Overnight is strongly preferred to avoid potential delays, which will negatively impact specimen quality) for arrival on Tuesday through Thursday at the ETCTN Biorepository at Nationwide Children's Hospital. Snap-frozen cores may be shipped Monday through Thursday, since the Biorepository does not need to perform additional time-sensitive pre-analytic processing

on them.

Other frozen specimens such as serum may be collected, processed and shipped to the ETCTN Biorepository on Monday through Thursday, since the Repository does not need to perform additional processing.

Fresh blood specimens may be collected and shipped Monday through Friday. Saturday delivery is only available for shipments of fresh blood.

9.2.1 Biopsy Collection Procedure (Formalin Kits)-Cores #1 And #2

Up to four core biopsies at least 1 cm in length will be obtained (if possible). Biopsies will be sent for analyses as defined in the protocol.

Note: Two cores (#1-2) biopsies will be fixed in formalin and placed in 70% Ethanol. Additional cores (#3) and (#4) will be immediately snap- frozen in vapor phase of Liquid Nitrogen (LN2) (see instructions below). If more than four biopsies are obtained, then additional biopsies will be collected in formalin and sent to the biorepository in 70% Ethanol for embedding. Kits are supplied by the ETCTN Biorepository only for specimens shipped to the Biorepository by the ETCTN Biorepository at Nationwide Children's Hospital. Kits should be ordered before specimen collection.

Standard Operating Procedure for collection of formalin-fixed specimen using kits (Core 1 and 2):

General Considerations:
Cores #1 and #2: Pre-label formalin specimen jars with the Rave generated specimen ID (which includes the protocol number and universal patient ID) and Intrinsic ID (See Specimen Tracking instructions below).

Specimen size requirement is as follows:
Surface area of 25mm^2 is optimal. Minimum is 5mm^2 and
Volume: 1mm^3 optimal. Minimum volume is 0.2mm^3.

Biopsy Collection Methodology:

9.2.1.1 Ensure that biopsies are only performed by qualified personnel. Follow institutional policies in collecting biopsies.

9.2.1.2 Ensure that specimen transportation to the pathology laboratory or designated processing laboratory is arranged to allow for quick tissue preservation.

9.2.1.3 Prior to specimen collection, ensure that all materials and equipment for collection and processing are ready for use, including prelabeling cassettes and formalin jars with the Rave generated specimen ID, Intrinsic ID, specimen type (e.g. P for primary, M for metastatic, and **B** for Baseline, **I** for Injected, AND **U** FOR Uninjected), and collection date.

9.2.1.4 Immediately transfer the first 2 core biopsy specimens into a specimen jar, containing 10% neutral-buffered formalin 30 mL (e.g., Leica 3800770 or similar, formalin provided by site), using one jar per core sample. Small or soft biopsies may be contained in a biopsy bag or tissue cassette to prevent specimen damage.

9.2.1.5 Perform fixation at room temperature (20-25°C). Record the date and time tissue added to formalin, and enter in the Comment field into the Sample Tracking System (Rave) for all submitted specimens. The optimal duration of fixation should be 16-24 hours by the time it is received at the ETCTN Biorepository.

9.2.1.6 After 24 hours of fixation in formalin, transfer the tissue cores to 70% Ethanol and ship the specimen to the ETCTN Biorepository (FedEx Priority Overnight required) for processing to allow for paraffin-embedding within 72 hours of time the tissue is held in Ethanol.

9.2.1.7 See section 9.5 for instructions for shipping to the ETCTN Biorepository at Nationwide Children's Hospital

9.2.2 *Collection of Snap-Frozen Biopsy (Cores #3 And #4)*

Pre-label the cryovial with the Rave generated specimen ID (which includes the protocol number and universal patient ID) and Intrinsic ID. (See Specimen Tracking instructions below).

The sites should follow the SOP described below for collection of snap-frozen tissue and make sure that they have required materials, reagents and equipment to collect the specimens.

1) Tissue should be frozen as soon as possible. Optimally, freeze within 30 minutes from collection.

2) Using clean forceps, place each of the second 2 core biopsy specimens into a pre-labeled cryovial.

3) Flash freeze each specimen contained in its cryovial using a dry ice/alcohol slurry or liquid nitrogen, according to institutional SOP. Keep frozen until shipment to ETCTN Biorepository.

4) Ship frozen specimens to the ETCTN Biorepository at Nationwide Children's Hopsital on the day of collection via FedEx Priority Overnight on dry ice in an insulated shipper or dual temperature-chambered kit.
5) See section 4.0 for instructions for shipping to the ETCTN Biorepository at Nationwide Children's Hospital.

9.2.3 *Whole Blood*

Whole blood collection in green-top tubes

1) Label 10-20 ml green-top (NaHep) tubes, Becton Dickinson Cat No. 367874 or equivalent, with Rave generated specimen ID (which includes the protocol number and Universal Patient ID), an Intrinsic ID, specimen type (blood), and collection date.
2) Collect 10-20 ml of peripheral blood in 10ml green-top (NaHep) tubes. **Collect 20 mL at Baseline, and 10 mL at Week 8 and Week 21-25.**
3) After collection, gently invert tube(s) 5-10 times to ensure adequate mixing of sodium heparin. Maintain specimens at ambient temperature (room temperature) during collection and transport.
4) **All green top tubes (or 10 mL of blood) will be shipped to the ETCTN Biorepository**.
5) See section 9.5 for instructions for shipping to the ETCTN Biorepository at Nationwide Children's Hospital.

Collection in cfDNA Streck tubes:

1) Label one 10 mL cfDNA Streck tube, with Rave generated specimen ID (which includes the protocol number and Universal Patient ID), an Intrinsic ID, specimen type (blood), and collection date.
2) At all-time points, collect 10 ml of blood into the pre-labeled tube an invert to mix. **Note: blood must be thoroughly mixed to ensure preservation of specimen.**
3) After collection, blood in cfDNA Streck tubes **should never be refrigerated**, as this will compromise the specimen**.** Blood collected in cfDNA Streck tubes is stable at room temperature.

Whole blood collection in K2 EDTA purple-top tubes

1) Collect 2 mL of peripheral blood into a labeled K2 EDTA Purple-Top Tube; each tube must be filled completely to ensure the correct blood/anticoagulant ratio.

2) After collection, gently invert tube(s) 8-10 times to ensure adequate mixing of EDTA. Maintain specimens at ambient temperature (room temperature) during collection and transport.
3) See section 4.0 for instructions for shipping to the ETCTN Biorepository at Nationwide Children's Hospital.

An external sample label should be fixed to the shipping container to alert the Biorepository of ***blood*** sample collection ***time*** and ***date*** (this helps to identify and prioritize received samples that have processing time requirements).

Blood should be shipped ambient FedEx Priority Overnight to the biorepository where it is processed the day of receipt ***within 24 hours of collection (not to exceed 48 hours)***.

9.3 Sample Tracking System Instructions

All biospecimens collected for this trial must be submitted using the ETCTN Rave Specimen Tracking System (STS) unless otherwise noted. The system is accessed through special Rave user roles: "CRA Specimen Tracking" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the Biorepository. Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website under the Rave/DQP tab.

Important: Failure to complete required fields in STS may result in a delay in sample processing. Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

For questions regarding the Specimen Tracking System, please contact the Theradex Help Desk at CTMSSupport@theradex.com.

A shipping manifest **must** be included with all sample submissions.

Pre-Analytic Information

Collection site must record all preanalytical information and enter the following into a specimen tracking system (STS) used by each trial network or record and provide with shipping manifest:

1) Time/date blood or tissue sample collection was made as ***Time/Date Specimen Collected***.
2) Ischemia start time (time when sample was devascularized OR estimated time of surgery)—***Tissue Collection Time/Date.***
3) Ischemic end time ***for each tissue core and surgical segment*** (time when sample was moved to preservative such as formalin or dry ice)—***Tissue Processing (Formalin Start) Time/Date.***
4) Completion of formalin fixation should be recorded as ***Formalin End Time/Date*** in the STS (or under "comments" if field is not available).
5) Start of 70% Ethanol dehydration should be recorded as ***Ethanol Start Time/Date*** in STS (or under "comments" if field is not available)
6) Time when fixed tissue, held in Ethanol, was placed into an automated processor should be recorded as ***Ethanol End Time/Date*** in the STS (or under "comments" if field is not available).
7) Core # for each core needle biopsy obtained. Each core should be recorded in the STS as a separate specimen with a unique Specimen ID that captures the chronological order in which the biopsy cores were obtained.

Biorepository will collect the following information for received specimens:

1) Date of sample receipt.
2) Time/date formalin-fixed tissue in Ethanol is moved into an automated processor—***recorded as Ethanol End Time.***
3) Record if frozen tissue sample arrived with insufficient amount of dry ice.
4) Collected pre-analytic information will be entered into the shipping manifest (NCI specimen tracking system).

9.3.1 Specimen Labeling

9.3.2.1 Blood Specimen Labels

Include the following on blood specimens (including whole blood and frozen, processed blood products – like serum and plasma):

- Patient study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (e.g. blood, serum)
- Collection date (to be added by hand)

9.3.2.2 Tissue Specimen Labels

Include the following on all tissue specimens or containers (e.g. formalin jar).

- Patient study ID

- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (e.g. FFPE Block, Formalin Fixed Tissue, Fresh Tissue in Media, *etc.*)
- Tissue type (P for primary or M for metastatic, and **B** for baseline, **I** for Injected, AND **U** FOR Uninjected)
- Surgical pathology ID (SPID) number
- Block number from the corresponding pathology report (archival only)
- Collection date (to be added by hand)

9.3.2.3 Example of Specimen Label

The following image is an example of a tissue specimen label printed on a standard Avery label that is 1" high and 2.625" wide.

The QR code in the above example is for the Specimen ID shown on the second line.
NOTE: The QR code label is currently under development at Theradex as of 31-Aug-2018; therefore, labels generated by the STS for this study may not include a QR code.

The second line item from the end includes four data points joined together:

1. Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (*e.g.*, for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none
4. The last alpha-numeric code is protocol specific and is only included if the protocol requires an additional special code classification

The last line on the example label is for the handwritten date and optional time.

9.3.2 Overview of Process at Treating Site

9.3.2.1 OPEN Registration

All registrations will be performed using the Oncology Patient Enrollment Network (OPEN)

system. OPEN communicates automatically with the Interactive Web Response System (IWRS) which handles identifier assignments, any study randomization and any prescribed slot assignments. If specimen analysis is required to determine eligibility, the protocol will be setup with multi-step registration.

Registration without eligibility specimen analysis:

1. Site enters registration data into OPEN during one or more steps.
2. IWRS receives data from OPEN, generates the Patient Study ID and the Universal Patient ID, both of which are sent back to OPEN.
3. IWRS sends all applicable registration data directly to Rave at the end of the final registration step.

Any data entry errors made during enrollment should be corrected in Rave.

9.3.2.2 Rave Specimen Tracking Process Steps

Step 1: Complete the **Histology and Disease** form (but do not upload reports until a specimen label can be applied to them) and the Baseline forms regarding **Prior Therapies**. Enter the initial clinical specimen data:

- **Specimen Tracking Enrollment** CRF**:** Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using report in EDC and collect specimen.

- Label specimen containers and write collection date on each label.
- After collection, store labeled specimens as described in Section.
- Apply an extra specimen label to *each* report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Molecular Reports (up to 4), Surgical reports and Pathology Verification form (when applicable). Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or specimen specific pathology or related report (one per specimen). Uploaded reports should have PHI data like name, mailing address, medical record number or SSN redacted. Do not redact SPID, block number or relevant dates.

Step 3: Complete specimen data entry.

- **Specimen Transmittal** Form**:** Enter Collection date and time and other required specimen details.

Step 4: When ready to ship, enter shipment information.

- **Shipping Status** CRF**:** Enter tracking number, your contact information, recipient, number of containers and ship date once for the 1st specimen in a shipment.
- **Copy Shipping** CRF**:** Select additional specimens to add to an existing shipment

referenced by the tracking number.

Step 5: Print shipping list report and prepare to ship.

- Print two copies of the shipping list, one to provide in the box, the other for your own records.
- Print pathology or other required reports to include in the box. Be sure the printed copy includes the specimen label.

Step 6: Send email notification.

- For only one of the specimens in the shipment, click "Send Email Alert" checkbox on the **Shipping Status** CRF to email recipient.

Step 7: Ship the specimen(s).

9.4 Shipping of Biospecimens from Clinical Sites to the ETCTN Biorepository

Shipping of Specimen(s):

Ambient temperature shipments: include core biopsies in formalin, blood in cfDNA Streck tube, and blood in green-top tubes (at Baseline only) in one shipment to the Biorepository on Monday through Wednesday, using the same box to ship that was used to receive the kit contents. Note: If blood is collected on Wednesday through Friday then it may be shipped separately from the tissue, on the day of collection.

- Place specimens (separated by specimen type) in zip-lock bags.
- Place zip-lock bags in a biohazard envelope containing absorbent materials. Next, place the biohazard envelope into a Tyvek envelope. Expel as much air as possible before sealing each envelope.
- Place the Tyvek envelope into the shipping container. In warm months, place a cold (NOT frozen) gel pack into the container with the specimens.
- Insert a copy of the shipping manifest and any other required paperwork, including operative and radiology, and/or pathology reports, into the container with the specimens. Place paperwork in a plastic zip-lock bag to prevent potential contamination in case of specimen leakage.
- Place the cover on the shipping container. Tape the shipping container closed with durable tape.
- Attach the FedEx air bill and attach to top of shipping container.
- Attach an Exempt Human Specimen sticker to the side of the shipping container.
- Make arrangements for courier pickup.

Frozen shipments: Serum (four aliquots) and snap-frozen core biopsies may be **c**ombined as one shipment on dry ice to the biorepository. Ensure that sufficient dry ice is included to completely encase the specimens to maintain specimen integrity during shipment. Frozen specimens may be shipped on Monday through Thursday.
Pre-fill the shipping container about 1/3 full with dry ice.
Place specimens (separated by specimen type) in zip-lock bags.
Place zip-lock bags in a biohazard envelope containing absorbent materials. Next, place the biohazard envelope into a Tyvek envelope. Expel as much air as possible before sealing each envelope.
Place the Tyvek envelope into the shipping container and fill the container to the top with additional dry ice.
Insert a copy of the shipping manifest and any other required paperwork, such as a pathology report, into the container with the specimens. Place paperwork in a plastic zip-lock bag in case of sample leakage.
Place the cover on the container. Tape the shipping container closed with durable tape.
Complete a FedEx air bill and attach to top of shipping container.
Complete a dry ice label.
Attach the dry ice label and an Exempt Human Specimen sticker to the side of the shipping container.
Make arrangements for courier pickup.
In cases of delays in shipment, store at -80 C.

Biorepository Shipping Address

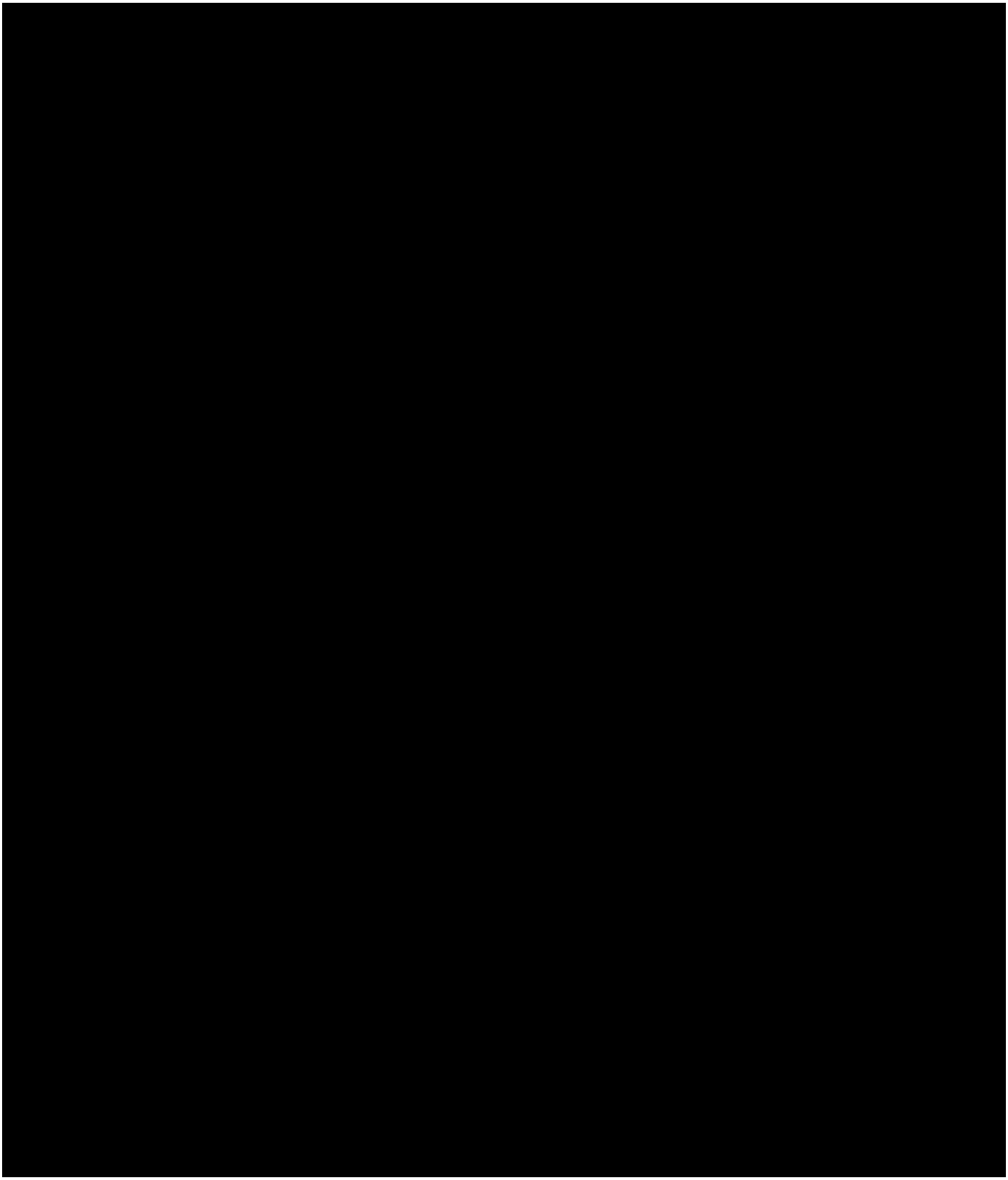
Ship to the address below. Ship formalin-fixed and fresh blood specimens the same day of specimen collection, when possible. Do not ship specimens the day before a holiday.

FedEx Priority Overnight is strongly recommended to prevent delay in package receipt.

ETCTN Biorepository
The Research Institute at Nationwide Children's Hospital
700 Children's Drive., WA1340
Columbus, Ohio 43205
PH: (614)-722-2865
FAX: (614)-722-2897
Email:BPCBank@nationwidechildrens.org

There is no central Courier account for this study. Sites are responsible for all costs for overnight shipments to the ETCTN Biorepository, utilizing the site screening and base intervention payments.

[redacted]



9.6 Integral Laboratory or Imaging Studies

NONE.

9.7 Investigational Device Information

NOT APPLICABLE.

[redacted]

9.9 Exploratory/Ancillary Correlative Studies

9.9.4 Whole Exome and RNA Sequencing

Specimens: Whole blood in NaHep (green-top) tubes at Baseline; tissue biopsy (-ies) fixed in formalin and submitted in 70% Ethanol to the ETCTN Biorepository at Baseline. Upon receipt, DNA will be extracted from K2-EDTA whole blood, aliquoted and stored in a -80°C freezer until distribution for testing. Tumor tissue will be processed and embedded. Slides will be cut, and the first section will be stained with H&E for pathology quality control review to assess tumor content; unstained slides will be macrodissected, if needed, and then DNA and RNA will be co-extracted, aliquoted, and stored in a -80°C freezer until distribution for testing.

This has been identified as the highest-priority exploratory study for the use of tumor biopsy tissue, after the integrated immunohistochemical studies.

Site(s) Performing Correlative Study: Sequencing will be performed at the Molecular Characterization Laboratory at NCI-Frederick. This laboratory is under the direction of Dr. P. Mickey Williams.

9.9.5 Immune phenotyping

Lymphocyte subsets in both tumor isolates and peripheral blood will be analyzed by multi-color flow cytometry.

[redacted]

9.9.6 *Additional Correlative Studies*

Plasma processed from cfDNA Streck tubes will be stored for future analyses of serum HSV status and circulating nucleic acids in blood plasma.

If sufficient tumor tissue is obtained, then additional exploratory assays will be conducted to quantitate T-VEC DNA in tissue samples using a PCR-based method.

9.10 Exploratory Imaging Correlatives

Pelvic MRI

Outcome Measure: MRI pelvis will be obtained in all patients (as part of standard of care) at baseline and prior to surgery (wk 21 -25) or 8-10 weeks from completion of chemoradiation (in patients not undergoing surgery).

Method: The current MDACC imaging protocol for primary rectal cancer incorporates the use of high resolution T2 weighted images acquired in the axial plane perpendicular to the plane of the tumor. These images are acquired using a phased array coil and small field of view (16-18cm), which generates an in-plane resolution of 0.6-0.7 mm. In addition to anatomic information provided by T2 weighted images, we obtain diffusion weighted images which are used to generate apparent diffusion coefficient (ADC) maps. These are a surrogates for tumor cellularity and treatment response. This imaging technique enables an accurate assessment of depth of tumor invasion beyond the muscularis propria and relationship to the mesorectal fascia (potential CRM) with high accuracy and inter-observer agreement. In addition the T stage is assessed with an accuracy of 67-83% and moderate inter-observer agreement. In terms of assessment of response to chemo radiation; morphologic MR markers have been proposed based on high

resolution T2 weighted images to distinguish well from poor responders. However this approach is subject to significant inter-observer variability. When supplemented with DWI there is a significant improvement in accuracy and the prediction of complete response.

In the current trial, we tumors will be characterized into good and poor responders to enable binary comparison. mrTRG is based on similar principles to the pathologic TRG and is based on the degree of tumor replaced by fibrotic stroma on post-treatment pelvic MRI. mrTRG-5 (no fibrosis, only tumor signal visible), mrTRG4 (predominantly tumor signal with minimal fibrotic single) will be defined as poor responders whereas mrTRG-1 (no tumor signal) to mrTRG-3 (50%or greater fibrotic stroma) will be defined as good. For the purposes of CRM, a margin greater than or equal to 1 mm between the tumor and the resection margin will be defined as clear (good responder) and the rest as poor responders. Prognosis of good responders including DFS, OS and local recurrence will be compared to that of poor responders. Furthermore, mrTRG will be compared to ypTRG to validate its accuracy. Two radiologists with extensive experience with rectal MRIs (Drs. Randy Ernst & Harmeet Kaur) will read all the scans to minimize inter-observer variability.

9.11 Exploratory genomic studies

Genomic testing results including but not limited to RAS, RAF mutations and / or microsatellite instability will be utilized to correlate with radiographic & pathologic response to talimogene laherparepvec based therapy, survival including DFS and OS. Mutation testing will be performed utilizing institutional next generation sequencing platform. Microsatellite status will be determined by either analysis of mismatch repair protein expression by immunohistochemistry or by microsatellite testing by polymerase chain reaction.

10. STUDY CALENDAR

Baseline evaluations (including laboratory tests) need not be repeated at start of protocol therapy if done within 1 week. Scans, x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. **On-study tests/visits** that must occur within a defined time frame shall have a standing window of allowance that is equal to +/- 2 days for any laboratory testing and +/- 4 days for any re-staging/disease assessment criteria. Surgery in eligible patients may occur within a window of + / - 2 weeks

	Pre-Study	Week 0	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8[g]	Wk 9/10 g	Wk 12/13 – 19/20m	Wk 27 - 36	Wk 27 & beyond[f]	Off Study[c]
TALIMOGENE LAHERPAREPVEC[B]		X			X		X		X						
FOLFOX[A]			X		X		X		X			X			
RT[k]											X				
Surgery[n]													X		
Informed consent	X														
Demographics	X														
Medical history	X														
Concurrent meds[h]	X		X----------											X	
Physical exam	X	X	X		X		X		X	X	X	X			X
Vital signs	X	X	X		X		X		X	X	X	X			X
Height	X				X		X		X	X	X	X			
Weight	X		X		X		X		X	X	X	X			X
Performance status	X		X		X		X		X	X		X			X
CBC w/diff, plts	X	X	X		X		X		X	X		X			X
PT / INR / aPTT[d]	X	X													
Serum chemistry[a]	X	X	X		X		X		X	X		X			X
Tumor Markers[e]	X												X		
EKG (as indicated)	X														
Adverse event evaluation[h]	X		X----------												X
Tumor measurements	X		In addition to baseline, tumor measurements will be obtained prior to surgery (wk 21-25). Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X
Radiologic evaluation	X		In addition to baseline, radiographic evaluation will be obtained prior to surgery (wk 21-25).												X
B-HCG	X[b]														
	CORRELATIVE STUDIES														
Archival Tissue	X														

Pelvic MRI	X												X		
Tumor Biopsies[i]			X[j]						X				X		
Peripheral Blood[l]	X								X				X		

A: FOLFOX: Dose as assigned*; administration schedule*
B: TALIMOGENE LAHERPAREPVEC: Dose as assigned*; administration schedule*
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
b: Serum pregnancy test (women of childbearing potential).
c: Off-study evaluation.
d. At baseline and subsequently as required per treating physician's discretion
e. Tumor markers include CEA and CA 19-9 at baseline, if above normal, repeat within 1 week of day 1 of radiation and with presurgical evaluation
f. Chemotherapy regimen / dosing / schedule, imaging and follow up post-surgery per treating physician's discretion
g. Evaluation by any involved provider (medical oncology / surgical oncology and / or radiation oncology)
h. Adverse event evaluation until 4 weeks out of surgery
i. Optional
j. In patients without adequate archival tissue
k. Radiation will be 25 Gy over 5 fractions.
l. Refer to Section 9 for tube types and volumes.
m. On day 1 of each cycle of FOLFOX
n. In those deemed needing surgical resection per clinical evaluation; not mandatory per protocol

11. MEASUREMENT OF EFFECT

Although the clinical benefit of these drugs has not yet been established, the intent of offering this treatment is to provide a possible additional therapeutic benefit to the known benefit of concurrent chemoradiation therapy to primary rectal cancer for palliation of symptoms and reduction in tumor burden. Thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients will be re-evaluated prior to surgery. In patients with completely resected tumors, further evaluation for disease recurrence will follow standard NCCN/ASCO guidelines and can be modified based on clinical symptoms at the treating physician's discretion. In surgically resected patients, disease-free survival and overall survival will be evaluated. In patients with metastatic disease at the time of treatment, overall survival will be evaluated in addition to response at distant sites (by diagnostic imaging) due to potential abscopal effect.

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be evaluated per study calendar (section 10).

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with talimogene laherparepvec.

Evaluable for objective response. All patients who start treatment will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately

measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). 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 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic 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 non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, 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 organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then 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 any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment 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 is preferred to evaluation by 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 (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray **Lesions** on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), 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).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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 at 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, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET 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:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. 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.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

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 (<1 cm).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the 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 (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

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.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm

[<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥Not Required**
CR	Non-CR/Non-PD	No	PR	≥Not Required**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Not Required**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Not Required as some patients may go to surgery and / or pursue other systemic therapies.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Progression-Free Survival

Include this section if time to progression or progression-free survival (PFS) is to be used. PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

Response Review

For trials where the response rate is the primary endpoint, it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best

approach.

11.2 Antitumor Effect – Hematologic Tumors

Please provide appropriate criteria for evaluation of response and methods of measurement.

11.3 Other Response Parameters

Other endpoints and the criteria for their measurement should be entered below or reference should be made to the protocol section where these criteria may be found.

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

For the Phase 1 portion of this study, all decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol Principal Investigator through the CTMS/IWRS. In addition, for the Phase 1 portion, the Protocol Principal Investigator will have at least monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and adverse events and unanticipated problems.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution’s data safety monitoring plan.

12.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (https://eapps-ctep.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Rave Read-Only, Rave CRA(Lab Admin), Rave SLA or Rave Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or Rave CRA (Lab Admin), the user must hold a minimum of an AP registration type. To hold the Rave Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.2.1 Method

CTMS Comprehensive *Monitoring:*
This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each

ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (phase 1 trials) the recommended phase 2 dose (RP2D), and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

12.3 CTEP Multicenter Guidelines

N/A

12.4 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to

Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

12.5 Genomic Data Sharing Plan

*If genomic data will be studied, analyzed, collected, and stored in an NIH/NCI Genomic Data Biorepository (*e.g.*, dbGaP, Cancer Genomic Database, other), please describe the genomic data sharing plan for this trial. Please refer to the NCI Genomic Data Sharing Policy at http://www.cancer.gov/grants-training/grants-management/nci-policies/genomic-data for considerations regarding the sharing of data, protection of patient confidential information, and the provision of adequate information in the patient informed consent.*

13. STATISTICAL CONSIDERATIONS

13.1 **Study Design/Endpoints**

Primary Endpoint:

To determine the dose limiting toxicities and maximum tolerated dose of TALIMOGENE LAHERPAREPVEC in combination with chemotherapy and radiation in rectal cancer

Study Design:

Chemoradiation will be at current standard of care doses i.e. 50.4 Gy over 28 fractions in combination with capecitabine 825 mg/m^2 po bid, days of radiation only (M-F). TALIMOGENE LAHERPAREPVEC will be escalated in 2 dose levels (PFU /ml) as indicated below using a standard 3 + 3 design.

- Talimogene laherparepvec will be administered via endoscopy by a qualified physician for a total of 4 doses at the following time points: a) week 1 prior to initiation of FOLFOX chemotherapy b) weeks 2-4 during FOLFOX chemotherapy c) week 6 d) week 8-9 during chemoradiation

- The first cohort of 3 patients will be treated at dose level 1.
- The next cohort of patients will not be treated until toxicity has been evaluated in the current cohort of patients.
- The algorithm is as follows: (1) If 0 out of 3 patients experiences dose-limiting toxicity (DLT), the next cohort of 3 patients will be treated at the next higher dose level. (2) If 1 out of 3 patients develops DLT, additional 3 patients will be treated at the same dose level. If no more DLT develops at the dose, i.e. 1 out of a total of 6 patients develops DLT, the dose escalation continues to next higher level for a cohort of 3 patients. (3) At any given dose, if more than 1 out of 3 patients or 6 patients experience DLT, the dose level exceeds the MTD and 3 patients will be treated at the next lower dose level if there are less than 6 patients already treated at that dose. If this is the lowest dose level tested, the trial will be terminated and MTD is not found. Following the above algorithm, MTD is defined as the highest dose level in which 6 patients have been treated with at most 1 instance of DLT

Dose level	**TALIMOGENE LAHERPAREPVEC Dose (PFU/ml)**	**Capecitabine (mg/m^2 po bid on days of radiation)**	**Radiation**
1	10^6, 10^7, 10^7,10^7	825	50.4 gray in 28 fractions
2	10^6, 10^8, 10^8,10^8	825	50.4 gray in 28 fractions

Based on the 3+3 design, the MTD is defined as the highest dose level in which 6 patients have been treated with at most 1 instance of DLT. Thus the target DLT rate is <=16.7%. The study only includes two dose levels, and the following table shows the operating characteristics of the 3+3 design under four different scenarios. For each scenario, the % time selecting a dose as the MTD, the average sample size treated at each dose level, and the probability of stopping the trial early are presented.

Scenario	**Doses**	**1**	**2**
#1	**Trued DLT**	**0.10**	**0.17**
	% MTD	**21%**	**70%**
	Average # patients	**3.7**	**3.7**
	Prob(early stopping)	**0.1**	
#2	**Trued DLT**	**0.10**	**0.25**
	% MTD	**36%**	**57%**
	Average # patients	**3.8**	**3.9**
	Prob(early stopping)	**0.08**	
#3	**Trued DLT**	**0.40**	**0.50**
	% MTD	**26%**	**5%**
	Average # patients	**4.3**	**1.3**
	Prob(early stopping)	**0.69**	
#4	**Trued DLT**	**0.05**	**0.10**
	% MTD	**9%**	**88%**
	Average # patients	**3.4**	**3.6**
	Prob(early stopping)	**0.02**	

Given the novelty and complexity of this study, a review of the data with the sponsor will occur before initiation of new dose levels. A total of 15 patients will be treated at the MTD (including the 6 from dose escalation phase and an addition 9 patients in expansion cohort) to assess safety of this dose level. Up to 15 patients (including the 6 patients treated at the MTD during dose escalation) will be enrolled into the expansion cohort to further confirm the safety of the MTD (as described in the study primary objective) and to assess efficacy and biomarker change (as described in the study secondary & exploratory objectives). With a total sample size of 15 and assuming the true DLT rate is 0.167, then the probability of observing at least one DLT event is 93.5%. If the true DLT rate is 0.30, then the probability of observing at least one DLT event is 99.5%. The MTD will be deemed to be recommended phase II dose (RP2D) if ≥ 80% of the patients are able to receive ≥ 80% of the planned treatment doses. If ≥ 1/3 of all patients at this dose experience DLTs, enrollment will be stopped and the Principal Investigator will discuss with all study investigators and with CTEP whether further addition of patients is needed to re-assess the RP2D. Monitoring of all safety and toxicity data is done by the Principal Investigator and the Corresponding Organization on a real-time basis as data are entered into Medidata Rave using the Web Reporting Module.

13.2 Sample Size/Accrual Rate

At least 2 patients and no more than 21 patients will be accrued onto this trial. Based on our prior experience, we estimate to identify 2-3 eligible patients per month.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	1	1	0	0	**2**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	2	3	0	0	**5**
White	3	4	2	2	**11**
More Than One Race	0	0	2	1	**3**
Total	**6**	**8**	**4**	**3**	**21**

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13.3 Stratification Factors

N/A

13.4 Analysis of Secondary Endpoints

Secondary objectives of the study include determining feasibility and NAR.. Feasibility will be reported in all patients who have started therapy as percent of planned dose intensity, NAR will be reported in all patients who undergo resection. NAR will be calculated as detailed in section 2.6 and will be reported using descriptive statistics. pCR will be reported with proportions along with the appropriate confidence intervals and survival by Kaplan-Meier method. Descriptive statistics will be used to report results of other correlative studies discussed above. Tumors will

be characterized into good and poor responders to enable binary comparison. mrTRG is based on similar principles to the pathologic TRG and is based on the degree of tumor replaced by fibrotic stroma on post-treatment pelvic MRI. mrTRG-5 (no fibrosis, only tumor signal visible), mrTRG4 (predominantly tumor signal with minimal fibrotic single) will be defined as poor responders whereas mrTRG-1 (no tumor signal) to mrTRG-3 (50%or greater fibrotic stroma) will be defined as good. For the purposes of CRM, a margin greater than or equal to 1 mm between the tumor and the resection margin will be defined as clear (good responder) and the rest as poor responders. Prognosis of good responders including DFS, OS and local recurrence will be compared to that of poor responders. Furthermore, mrTRG will be compared to histological TRG (ypTRG)to validate its accuracy. Two radiologists with extensive experience with rectal MRIs (Drs. Randy Ernst & Harmeet Kaur) will read all the scans to minimize inter-observer variability.

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28. *Injection site reactions may include redness, swelling, and bleeding.*
29. *Pain can occur in the tumor, injection sites and nodal draining (axilla and groin etc) lymph nodes.*
30. *Several events which are autoimmune-mediated, such as acute kidney injury (acute renal failure), glomerulonephritis (nephritis), worsening of psoriasis, pneumonitis, vasculitis, and vitiligo (areas of skin with loss of color) have been observed in clinical trials of talimogene laherparepvec.*
31. *Skin infection (cellulitis) can be complicated with local and systemic infection, tissue necrosis, and ulceration, or wound complications.*
32. *Obstructive airway disorder has occurred in one patient with Squamous cell carcinoma of the head and neck (SCCHN) with a suproventricular mass who developed acute respiratory distress requiring a trachetomy 13 days after the second dose of talimogene laherparepvec. Imaging showed a mass in the larynx and adjacent lymph nodes on the contralateral side.*
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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B INFORMATION FOR PATIENTS, THEIR CAREGIVERS, AND NON-STUDY HEALTHCARE TEAM ON POSSIBLE INTERACTIONS WITH OTHER DRUGS AND HERBAL SUPPLEMENTS

The patient _____ is enrolled on a clinical trial using the experimental study drug, talimogene laherparepvec. In this trial, talimogene laherparepvec is given along with other chemotherapy drugs including capecitabine, 5-FU and oxaliplatin. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Capecitabine (and to a lesser extent fluorouracil) interacts with certain specific enzyme(s) in your liver.

- The enzyme in question is **cytochrome P450**, and capecitabine and fluorouracil may reduce the activity of this enzyme. For this reason, while receiving these medications, the levels of other medications cleared by these enzymes may be increased.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Talimogene laherparepvec and chemoradiation may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Capecitabine and to a lesser extent fluorouracil must be used very carefully with other medicines that use cytochrome p450. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors or substrates of cytochrome P450

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Warfarin, allopurinol, cimetidine, sorivudine, brivudine and phenytoin are known to interact with capecitabine and to a lesser extent with fluorouracil. Speak to your doctors or pharmacist if you need to be on these medications at the same time.
- Since antiviral medications including but not limited to acyclovir may decrease the efficacy of talimogene laherparepvec, do not start these medications without discussing with your health care team first.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is Dr. Arvind Dasari at and he can be contacted at 713-792-2828

APPENDIX C-1 INFORMATION SHEET FOR PATIENTS RECEIVING TALIMOGENE LAHERPAREPVEC

Study Title:_____

NCI protocol #:_____ Amgen Tracking #:_____

The patient _____ is enrolled on the clinical trial above using the experimental drug **Talimogene laherparepvec(talimogene laherparepvec)**. This clinical trial is sponsored by the National Cancer Institute.

The PI Name:_____ and PI contact # _____

This form is addressed to the patient, but includes important information for others who care for this patient.

Dear Patient:

*This Information Sheet is being provided to patients who has been enrolled in a clinical trial of Talimogene laherparepvec(talimogene laherparepvec**). A separate Information Sheet is also being provided for you close contacts and Healthcare Providers not involved in the trial. A close contact is considered a person that lives with the Patient (household member), care-giver, sex partner, or shares a bed with the Patient or conducts other activities that could involve exchange of bodily fluids through close physical contact.*

The purpose of this Sheet is to inform you of 1) ***Potential risk of exposure to talimogene laherparepvec***, 2) ***Precautions*** and 3) ***Instructions in the case of talimogene laherparepvec transmission***. In the end of this document, additional information is also provided for ***Instructions for talimogene laherparepvec injected sites care***.

I. What is the Study Drug, Talimogene laherparepvec(talimogene laherparepvec)?

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

II. Can talimogene laherparepvec be spread to family members or other close contacts?

Talimogene laherparepvec could potentially be spread to family or people who have close physical or

intimate contact with the Patient after tumor(s) are injected with the study drug. So far there have been no reported cases in clinical trial participants who have received talimogene laherparepvec of spreading talimogene laherparepvec to family members or other close contacts. In clinical trials so far, no talimogene laherparepvec has been detected outside of the dressing that is placed on top of the site where it was injected.

The naturally occurring herpes simplex virus is not transmitted through the air or water droplets (such as when coughing or sneezing). Spreading occurs through direct contact from one person to another, particularly if a cold sore or genital sore is present (for example, through kissing or having sexual intercourse or other intimate contact). It may also be spread by sharing a razor, towel, dish that has come in contact with a sore or bodily fluids..

Spreading (transmission) of talimogene laherparepvec may be similar to spreading of the naturally occurring herpes simplex virus, and spreading may be more likely if you have a break in your skin or a mucous membrane comes into contact with an injection site or body fluids of a treated patient. Unlike the naturally occurring virus, however, talimogene laherparepvec is administered into tumor lesions and is not expected to be able to replicate effectively in other noncancerous tissues. There have been no cases of spreading of talimogene laherparepvec to close contacts reported in clinical studies to date.

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

It is unknown if talimogene laherparepvec is shed through stool. Patients should consider using precautions while using shared toilet facilities such as; wearing gloves while using a shared roll of toilet paper or a separate roll and thoroughly washing hands and wiping the toilet seat or any other areas that may potentially be contaminated with a disinfectant wipe.

It is not known if talimogene laherparepvec virus can appear in mucous membranes of the lips and mouth or genitals of treated subjects. A clinical study is ongoing to determine if talimogene laherparepvec can be detected in the mouth area and genital area of treated subjects.

To reduce the risk of exposure to and transmission of talimogene laherparepvec, please read carefully the Instructions below.

III. Who Should Not Have Contact with talimogene laherparepvec?

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

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

IV. What Precautions Should Be Taken to Avoid Being Exposed to talimogene laherparepvec?

- Avoid direct contact with the treated patient's injection sites and body fluids.
- Wear gloves if changing dressings which cover the treated patient's injection sites.
- Place all used dressings and cleaning materials in a sealed, plastic bag, and throw them away as household waste or return to the study site for disposal depending on local guidance.
- The patient should avoid touching or scratching the injection site.

- If you notice any weeping or oozing from the injection site, please contact your healthcare team. (please also refer to **Instructions for talimogene laherparepvec Injection Site Care**)
- Observe proper hygiene (wash hands with warm water and soap after touching the injected lesions or handling the dressings) to avoid spreading talimogene laherparepvec to other persons. If there is direct contact with the injected sites, you should clean the affected area on your body with soap and water and/or a disinfectant.
- If the treated subject develops any mouth or genital herpetic lesions (for example a painful fluid filled blister) during treatment with talimogene laherparepvec or during the follow-up period of the clinical trial, they should avoid activities that could increase the possibility of transmission such as sharing straws, drinking glasses or engaging in sexual activity until the lesions fully resolve.
- The naturally occurring herpes simplex virus (HSV-1) can be transmitted through sexual contact. It is not known if talimogene laherparepvec will behave the same way, thus treated subjects or their partners should use a latex condom when engaging in sexual activity to prevent possible transmission of talimogene laherparepvec during the treatment with talimogene laherparepvec and until 30 days after the end of treatment. For those with latex allergies, polyurethane condoms may be used.

V. What Can Happen if Family Members or Close Contacts are Exposed to talimogene laherparepvec?

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

If talimogene laherparepvec were transmitted from a talimogene laherparepvec treated patients to a third party, the potential symptoms might be similar to those of the naturally occurring herpes simplex virus such as:

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

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

Persons should seek a healthcare provider for signs of systems suggestive of herpes infection occur. talimogene laherparepvec is sensitive to the antiviral drug acyclovir and any possible infection may be treated with this drug in its usual doses by your doctor.

VI. INSTRUCTIONS for Reporting of Suspected talimogene laherparepvec Exposure or Infection:

1) **Instructions for <u>patients treated with talimogene laherparepvec</u>:** If you develop symptoms of herpes infection:
    - **IMMEDIATELY** inform the talimogene laherparepvec trial doctor by contacting: **<<insert study site contact>>.** The talimogene laherparepvec trial doctor will provide further instructions for management and evaluation. You doctor may need to obtain test for the virus within 3 days of your notification of the symptoms
    - If you are seeing a doctor who is not part of the clinical trial, please give this information sheet to the Doctor and have them contact the talimogene laherparepvec trial staff: **<<insert study site contact>>.**
2) **Instructions for <u>Close Contact or non-study Healthcare providers</u> with suspected exposure to talimogene laherparepvec**:
    - Please refer to the Information Sheet for Close Contacts.

APPENDIX C-2 INFORMATION SHEET FOR FAMILY MEMBERS, CLOSE CONTACTS OF PATIENTS RECEIVING TALIMOGENE LAHERPAREPVEC ON CLINICAL TRIALS, AND FOR NON-STUDY (NOT INVOLVED IN THE TALIMOGENE LAHERPAREPVEC TRIALS) HEALTH CARE PROVIDERS (HCP)

Study Title:_____

NCI protocol #:_____ Amgen Tracking #:_____

The patient _____ is enrolled on the clinical trial above using the experimental drug **Talimogene laherparepvec(talimogene laherparepvec)**. This clinical trial is sponsored by the National Cancer Institute.

The PI Name:_____ and PI contact # _____

Dear Family Members, Caregivers, other Close Contacts and non-study Healthcare Providers:

*This Information Sheet is being provided to patients who has been enrolled in a clinical trial of Talimogene laherparepvec(talimogene laherparepvec)**,** and their close contacts and Healthcare Providers not involved in the trial**.** A close contact is considered a person that lives with the Patient (household member), care-giver, sex partner, or shares a bed with the Patient or conducts other activities that could involve exchange of bodily fluids through close physical contact. Non-study HCP are HCPs not involved in the talimogene laherparepvec clinical trials but are seeing patients receiving talimogene laherparepvec or their close contacts.*

The purpose of this Sheet is to inform you of 1) ***Potential risk of exposure to talimogene laherparepvec***, 2) ***Precautions*** and 3) ***Instructions in the case of talimogene laherparepvec transmission***. In the end of this document, Additional information about talimogene laherparepvec for Healthcare Providers who are not involved in this trial

I. What is the Study Drug, Talimogene laherparepvec(talimogene laherparepvec)?

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

II. Can talimogene laherparepvec be spread to family members or other close contacts?

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

The naturally occurring herpes simplex virus is not transmitted through the air or water droplets (such as when coughing or sneezing). Spreading occurs through direct contact from one person to another, particularly if a cold sore or genital sore is present (for example, through kissing or having sexual intercourse or other intimate contact). It may also be spread by sharing a razor, towel, dish that has come in contact with a sore or bodily fluids..

Spreading (transmission) of talimogene laherparepvec may be similar to spreading of the naturally

occurring herpes simplex virus, and spreading may be more likely if you have a break in your skin or a mucous membrane comes into contact with an injection site or body fluids of a treated patient. Unlike the naturally occurring virus, however, talimogene laherparepvec is administered into tumor lesions and is not expected to be able to replicate effectively in other noncancerous tissues. There have been no cases of spreading of talimogene laherparepvec to close contacts reported in clinical studies to date.

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

It is not known if talimogene laherparepvec virus can appear in mucous membranes of the lips and mouth or genitals of treated subjects. A clinical study is ongoing to determine if talimogene laherparepvec can be detected in the mouth area and genital area of treated subjects.

To reduce the risk of exposure to and transmission of talimogene laherparepvec, please read carefully the Instructions below.

III. Who Should Not Have Contact with talimogene laherparepvec?

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

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

IV. What Precautions Should Be Taken to Avoid Being Exposed to talimogene laherparepvec?

- Avoid direct contact with the treated patient's injection sites and body fluids.
- Wear gloves if changing dressings which cover the treated patient's injection sites.
- Place all used dressings and cleaning materials in a sealed, plastic bag, and throw them away as household waste or return to the study site for disposal depending on local guidance.
- The patient should avoid touching or scratching the injection site.
- The injection sites should be covered for at least 7 days after the last injection with watertight dressings which allow for air exchange. If the dressing comes loose or falls off prior to 7 days after the injection, it should be replaced right away with a clean dressing. However, you may need to keep the dressing on longer if the lesions at the injection sites are weeping or oozing. (please also refer to **Instructions for talimogene laherparepvec Injection Site Care**)
- Observe proper hygiene (wash hands with warm water and soap after touching the injected lesions or handling the dressings) to avoid spreading talimogene laherparepvec to other persons. If there is direct contact with the injected sites, you should clean the affected area on your body with soap and water and/or a disinfectant.
- If the treated subject develops any mouth or genital herpetic lesions (for example a painful fluid filled blister) during treatment with talimogene laherparepvec or during the follow-up period of the clinical trial, they should avoid activities that could increase the possibility of transmission such as sharing straws, drinking glasses or engaging in sexual activity until the lesions fully resolve.
- The naturally occurring herpes simplex virus (HSV-1) can be transmitted through sexual contact. It is not known if talimogene laherparepvec will behave the same way, thus treated subjects or their partners should use a latex condom when engaging in sexual activity to prevent possible

transmission of talimogene laherparepvec during the treatment with talimogene laherparepvec and until 30 days after the end of treatment. For those with latex allergies, polyurethane condoms may be used.

V. What Can Happen if Family Members or Close Contacts are Exposed to talimogene laherparepvec?

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

If talimogene laherparepvec were transmitted from a talimogene laherparepvec treated patients to a third party, the potential symptoms might be similar to those of the naturally occurring herpes simplex virus such as:

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

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

Persons should seek a healthcare provider for signs of systems suggestive of herpes infection occur. talimogene laherparepvec is sensitive to the antiviral drug acyclovir and any possible infection may be treated with this drug in its usual doses by your doctor.

VI. INSTRUCTIONS for Reporting of Suspected talimogene laherparepvec Exposure or Infection:

1) **Instructions for <u>Close Contact</u> with suspected exposure to talimogene laherparepvec**: If a close contact or non-study HCP is suspected to have been exposed to talimogene laherparepvec (e.g. symptoms suggestive of herpes infection or contact of open skin/mucosa with talimogene laherparepvec), **you should inform the individuals below** and seek medical attention. Your doctor may want to determine if talimogene laherparepvec is present, depending on the symptoms observed. For example if a cold sore appears, a swab may be taken for analysis. These tests will be most reliable if done within the first 3 days of symptoms occurring, but you should report to your health care provider at any time symptoms appear. Before any samples or information about your health or symptoms is collected your authorization will be requested in writing.

    1. **Call the Amgen Call Center** at 1-855-IMLYGIC (1-855-465-9442) immediately when the close contacts/HCP noticed symptoms/signs of herpes infection, as testing of the virus must occur within 3 days**.**

- Amgen will provide close contacts/HPC with instructions to seek medical consultations for management and potentially for talimogene laherparepvec DNA test. The talimogene laherparepvec DNA test must be done within three days of the appearance of the symptoms.
- The physicians of Close Contacts will be responsible for obtaining the swab of herpetic lesions submit it to talimogene laherparepvec testing, per instructions from Amgen.
- The Amgen Call Center is open 24 hours a day, 7 days a week (24/7). Please have this Information Sheet handy when you call Amgen.

2. Also **inform the talimogene laherparepvec clinical trial doctor** of the incident by contacting: **<<insert study site contact>>**.
3. When seeing a doctor for your symptom or talimogene laherparepvec exposure, please give this Information Sheet to the Doctor.

APPENDIX D BIOASSAY TEMPLATES

NA

APPENDIX E NCI TEMPERATURE EXPOSURE LOG

Talimogene laherparepvec (NSC 785349)

NCI Protocol Number: _____

PMB Order Number: _____ (obtain from Shipment Record)

Date Received: _____

Maximum exposure time: **90 Seconds**
Exposure Time
Start Time = time inner shipping container lid is removed
Stop Time = time --80ºC freezer door is closed

Start Time: _____:_____:_____ (hour:minute:second - example: 09:50:01)
Stop Time: _____:_____:_____ (hour:minute:second - example: 09:50:58)

Confirm time difference from start time to stop time does not exceed 90 seconds:
□ YES □ NO

Comments: _____

Name: _____ Date: _____

Complete one log for each shipping container received.
Retain log with your study records. If exposure time exceeds 90 seconds, quarantine the agent supplies in the -80ºC freezer and call PMB immediately at 240-276-6575 for guidance.

APPENDIX F RECEIVING INSTRUCTIONS FOR NCI SUPPLIED TALIMOGENE LAHERPARECVEC (NSC 785349)

IMPORTANT: READ THE ENTIRE INSTRUCTIONS BEFORE OPENING THE INNER SHIPPING CONTAINER

Step 1: Verify all shipment documents are present:

- NCI Shipment Record of Clinical Drug Request
- Temperature Exposure Log

Step 2: Transfer Talimogene laherparepvec vials to -80^{0}C (+/- 10^0 C) freezer

You have 90 seconds to verify the contents of the shipping container and place the agent supplies in the -80^{o}C freezer once the inner container lid is opened and the supply exposed to room temperature

- Place the shipping container near the -80^{o}C freezer
- Don gloves per your institutional procedures for handling dry ice
- Open the lid of the inner shipping container
- A second person should record the start time on the temperature exposure log once the lid of inner shipping container is removed
- Open the payload box sleeve and remove the payload box containing the carton(s) of Talimogene laherparepvec
- Open the payload box and remove carton(s) of Talimogene laherparepvec
- Verify agent, strength, quantity and lot number received against NCI Shipment Record of Clinical Drug Request
- Place carton(s) of Talimogene laherparepvec in the -80^{o}C freezer and close the freezer door
- Record the stop time on the temperature exposure log

Step 3: Complete documentation

- Confirm the time difference from start time to stop time does not exceed 90 seconds
- Complete remainder for temperature exposure log and retain with your study records
- If exposure time exceeds 90 seconds, quarantine the agent supplies in the -80^{0}C (+/- 10^0 C) freezer and call PMB immediately at 240-276-6575 for guidance.

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27. *This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.*
28. *Injection site reactions may include redness, swelling, and bleeding.*
29. *Pain can occur in the tumor, injection sites and nodal draining (axilla and groin etc) lymph nodes.*
30. *Several events which are autoimmune-mediated, such as acute kidney injury (acute renal failure), glomerulonephritis (nephritis), worsening of psoriasis, pneumonitis, vasculitis, and vitiligo (areas of skin with loss of color) have been observed in clinical trials of talimogene laherparepvec.*
31. *Skin infection (cellulitis) can be complicated with local and systemic infection, tissue necrosis, and ulceration, or wound complications.*
32. *Obstructive airway disorder has occurred in one patient with Squamous cell carcinoma of the head and neck (SCCHN) with a suproventricular mass who developed acute respiratory distress requiring a trachetomy 13 days after the second dose of talimogene laherparepvec. Imaging showed a mass in the larynx and adjacent lymph nodes on the contralateral side.*

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