Abbreviated Title: Pexa-Vec Colorectal Ca

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Title: A Phase I/II study of Pexa-Vec Oncolytic Virus in Combination with Immune Checkpoint Inhibition in Refractory Colorectal Cancer.

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Investigational Agents:

Drug Name:	Tremelimumab; Durvalumab; Pexastimogene Devacirepvec (Pexa-Vec)
BB IND Number:	17363
Sponsor:	Center for Cancer Research, National Cancer Institute
Manufacturers:	MedImmune/AstraZeneca Sillajen Inc.

PRÉCIS

Background:

- Immune-based approaches in colorectal cancer have unfortunately – with the notable exception of immune checkpoint inhibition in microsatellite instable (MSI-hi) disease – been largely unsuccessful. The reasons for this are unclear but no doubt relate to the fact that in advanced disease colorectal cancer appears to be less immunogenic, as evidenced by the lack of infiltrating lymphocytes with advancing T stage
- Pexa-Vec (JX-594) is a thymidine kinase gene-inactivated oncolytic vaccinia virus engineered for the expression of transgenes encoding human granulocyte- macrophage colony-stimulating factor (GM-CSF) and β-galactosidase. Apart from the direct oncolytic activity, oncolytic viruses such as Pexa-Vec have been shown to mediate tumor cell death via the induction of innate and adaptive immune responses
- Tremelimumab is a fully human monoclonal antibody that binds to CTLA-4 expressed on the surface of activated T lymphocytes and causes inhibition of B7-CTLA-4-mediated downregulation of T-cell activation. Durvalumab is a human monoclonal antibody directed against PD-L1.
- The aim of the study is to evaluate whether the anti-tumor immunity induced by Pexa-Vec oncolytic viral therapy can be enhanced by immune checkpoint inhibition.

Objective:

- To determine the safety, tolerability and feasibility of Pexa-Vec oncolytic virus in combination with immune checkpoint inhibition in patients with refractory metastatic colorectal cancer.

Eligibility:

- Histologically confirmed metastatic colorectal cancer.
- Patients must have progressed on, been intolerant of or refused prior oxaliplatin- and irinotecan-containing, fluorouracil-based, chemotherapeutic regimen and have disease that is not amenable to potentially curative resection. Patients who have a known KRAS wild type tumor must have progressed, been intolerant of or refused cetuximab or panitumumab-based chemotherapy.
- Patients tumors must be documented to be microsatellite-stable (MSS) either by genetic analysis or immunohistochemistry OR microsatellite-high with documented disease progression following anti-PD1/PDL1 therapy.
- Patients must have at least one focus of metastatic disease that is amenable to pre- and on-treatment biopsy.
- Willingness to undergo mandatory tumor biopsy.

Design:

- The proposed study is Phase I/II study of Pexa-Vec oncolytic virus at two dose levels in combination with immune checkpoint inhibition in patients with metastatic colorectal cancer.

- Patients will receive Pexa-Vec, administered IV every 2 weeks for 4 doses, in 4 separate arms A1, A2, B1, and B2. The first administration will be on Day –(minus) 12, followed by administration on Days 2, 16 and 30 (i.e. 4 doses in total).
    - Arms A1 and A2: In addition to the oncolytic virus patients will also receive durvalumab at a flat dose of 1500 mg beginning on Day 1 followed by q28days until off-treatment criteria are met.
    - Arms B1 and B2: In addition to the oncolytic virus patients will also receive tremelimumab 300 mg and durvalumab 1500 mg on Day 1 followed by q28days subsequent continuation of the durvalumab alone until off-treatment criteria are met.
- All patients will undergo a baseline tumor biopsy and a post treatment biopsy.
- Accrual ceiling will be set at 35 to allow for patients replaceable for reasons other than toxicity.
- Patients will be restaged every 8 weeks +/- 3 days

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1 INTRODUCTION

1.1 Study Objectives

1.1.1 Primary Objective

- To determine the safety, tolerability and feasibility of Pexa-Vec oncolytic virus in combination with immune checkpoint inhibition in patients with refractory metastatic colorectal cancer.

1.1.2 Secondary Objectives:

- To determine the response rate (by RECIST 1.1) of Pexa-Vec oncolytic virus in combination with immune checkpoint inhibition in patients with refractory metastatic colorectal cancer.
- To evaluate the 5-month and overall progression-free survival and overall survival in patients with metastatic colorectal cancer during and following treatment with of Pexa-Vec oncolytic virus in combination with immune checkpoint inhibition in patients with refractory metastatic colorectal cancer.

1.1.3 Exploratory Objectives:

- To measure changes in immune parameters in the peripheral blood and tumors in patients with metastatic colorectal cancer during and following treatment with Pexa-Vec oncolytic virus in combination with immune checkpoint inhibition.

1.2 Background and Rationale

1.2.1 Metastatic colorectal cancer (CRC) and the current therapeutic paradigm

Colorectal cancer is a highly prevalent cancer, with approximately 300,000 new cases diagnosed annually in the U.S. and Europe. Over the past 10-15 years' new chemotherapeutics (oxaliplatin and irinotecan) in addition to so-called targeted agents (bevacizumab and cetuximab/panitumumab) have resulted in improvements in the median overall survival from 10-12 months to approximately 2 years. Once a patient progress after first line treatment however, the average survival is in the 12-14-month range, and a huge unmet need exists to improve options for patients with this disease.

Immune-based approaches in colorectal cancer have unfortunately – with the notable exception of immune checkpoint inhibition in MSI-hi[I] disease – been largely unsuccessful. The reasons for this are unclear but no doubt relate to the fact that in advanced disease colorectal cancer appears to be less immunogenic, as evidenced by the lack of infiltrating lymphocytes with advancing T stage[1, 2]. The prevalence of colorectal cancer and the high proportion of patients with metastatic disease who are microsatellite stable (85-90%) mean that this is a large territory of each oncology clinic for whom any advance in immunotherapy would be extremely significant. Given the apparent lack of intrinsic anti-tumor immunity in these patients, innovative immune-stimulative approaches are needed. Oncolytic virus technology falls into this category, their great potential being their ability to induce immunity in tumors[3] such as microsatellite-stable (MSS) colorectal cancer - where low mutagenic burden result in low endogenous immunity (and lack of single-agent activity to checkpoint inhibitors).

1.2.2 Pexa-Vec (pexastimogene devacirepvec; JX-594)

Oncolytic immunotherapy represents a novel therapeutic platform for the treatment of cancer with unique attributes compared to conventional chemotherapy. Oncolytic viruses are native or engineered viruses that preferentially replicate in and lyse cancer cells. Selective tumor cell replication is thought to depend on infection of neoplastic cells, which harbor low levels of protein kinase R (PKR) and dysfunctional type I IFN signaling elements. These changes allow more efficient viral replication, and with selected deletion of specific viral genes, replication in normal cells with activated PKR may not be possible. The FDA recently approved the first oncolytic virus for cancer [Talimogene laherparepvec (T-VEC)], for melanoma on October 15, 2015.

Pexa-Vec (JX-594) is a thymidine kinase gene-inactivated oncolytic vaccinia virus engineered for the expression of transgenes encoding human granulocyte- macrophage colony-stimulating factor (GM-CSF) and β-galactosidase. Most of the oncolytic clinical trials to date have involved intratumoral injection. Whilst Pexa-Vec can (and has been) also administered in this manner, it has the advantage of being able to be administered systemically by intravenous administration.

Clinical experience: More than 300 patients have been treated with Pexa-Vec administered either intravenously (IV), intratumorally (IT) or both IV and IT. In total, approximately 1200 patient doses of Pexa-Vec have been administered (IV and IT combined). Pexa-Vec treatment has generally been well-tolerated with main side effects being transient flu-like symptoms and transient hypotension. A randomized Phase 2a trial in HCC demonstrated a significant increase in OS at high dose Pexa-Vec versus low dose Pexa-Vec and a Phase 3 trial in first-line HCC is ongoing[4]. In a phase 1 trial of a single intravenous infusion of Pexa-Vec in 23 patients with advanced solid tumors, dose-related antitumor activity was observed and normal tissues were not affected clinically[5]. Pexa-Vec has been administered safely to patients with colorectal cancer with proof of concept for tumor penetration and selectivity[6]. Thus far, at least 60 patients with colorectal cancer have been treated across several Phase 1/2 studies, again demonstrating that Pexa-Vec therapy was well-tolerated. Reproducible infection of CRC metastases following IV Pexa-Vec was confirmed on post treatment biopsies[5].

The most common adverse events (AEs) reported with Pexa-Vec have been acute, transient flu-like symptoms, including fever and chills. Transient, hypotension responsive to fluid administration was also noted in a subset of patients within 24 hours of treatment. Pexa-Vec related skin pustules were observed in 22% (64/292) of patients receiving IV or IT treatments. Pustules developed after 9% (62/691) of IV infusions. The pustules were self-limited and resolved without sequela within 2-3 weeks of treatment, consistent with the timeline for pustule resolution utilizing wild-type vaccinia vaccine.

1.2.2.1 Phase 1b Study of Patients with Colorectal Cancer Treated Intravenously Every Two Weeks with Pexa-Vec

Fifteen patients with treatment- refractory colorectal cancer were enrolled on a phase 1b study of Pexa-Vec (also known as JX-594). Pexa-Vec was administered intravenously every 14 days, at dose levels of 1×10^6, 1×10^7, or 3×10^7 plaque-forming units (pfu)/kg. The primary endpoint was to determine the maximum tolerated dose. Secondary endpoints were pharmacokinetics and pharmacodynamics as well as antitumor activity. All patients received at least two Pexa-Vec doses. No dose-limiting toxicities were reported, and the maximum tolerated dose was not reached. The most common adverse events were grade 1/2 flu-like symptoms, generally lasting <24 hours. There

was some preliminary evidence of efficacy with the majority of patients (67%) having radiographically stable disease.

1.2.2.2 Phase 1/2a Study of Patients with Colorectal Carcinoma Treated Intravenously (IV) Weekly with Pexa-Vec Alone and in Combination with Irinotecan

A Phase 1/2a dose-escalation study of Pexa-Vec administered weekly alone or in combination with irinotecan in patients with Stage 4, chemotherapy refractory CRC has completed enrollment. A total of 52 patients received 5 IV doses of Pexa-Vec weekly at doses of $3x10^8$ pfu to $1x10^9$ pfu alone or in combination with irinotecan. Pexa-Vec alone and in combination with irinotecan was generally well-tolerated with no dose- limiting toxicities experienced.
Pexa-Vec has been well-tolerated in study patients with most AEs being mild-to- moderate in severity. The most common Pexa-Vec treatment related AEs identified as a percent of total patients treated included generally mild-to-moderate: pyrexia (94%), chills (84%), hypotension (62%), nausea (46%), and rash pustular (42%). No Grade 4 or 5 AEs related to treatment were reported.
The following Grade 3 AEs related to Pexa-Vec single-agent treatment were experienced by (3.6%, n = 1) of patient experienced each of the following: chills, hypotension, fatigue, hypertension, abdominal pain, blood bilirubin increased, cytokine release syndrome, hypoxia, ALT increased, AST increased, somnolence, and troponin increased. No Grade 4 or Grade 5 AEs related to Pexa-Vec were reported.

1.2.2.3 Other clinical trial data for Pexa-Vec

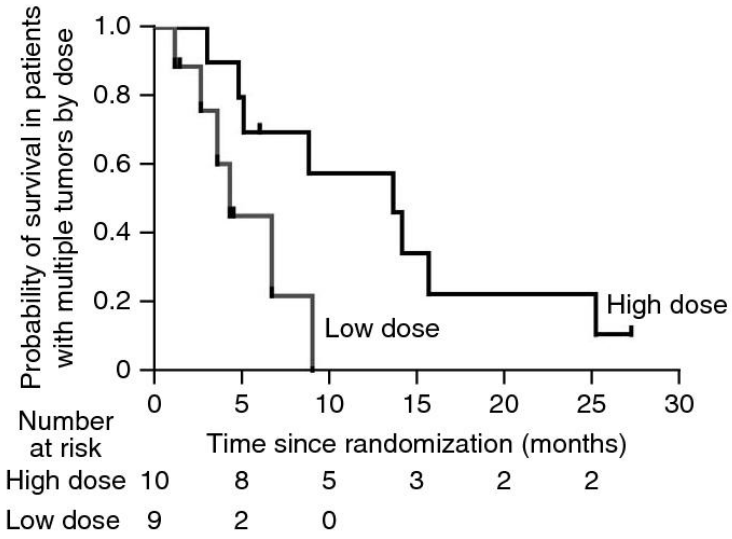
1.2.2.3.1 Phase 1 Liver Tumor Trial

A Phase 1 dose-escalation trial of Pexa-Vec in patients with primary or metastatic liver tumors (JX594-IT-HEP001) has been completed and the results published[6]. Pexa-Vec was administered by IT injection every 3 weeks in patients with refractory, injectable tumors within the liver at one of 4 dose levels (1×10^8 pfu to 3×10^9 pfu). Patients were scheduled to receive 2–4 treatments, but could subsequently receive an additional 4 treatments if there was evidence response or clinical benefit. Fourteen patients, including 3 HCC patients were enrolled and treated. Pexa-Vec was well-tolerated in study patients. All patients treated with Pexa-Vec experienced mild-to-moderate flu-like symptoms, which included fever, chills, anorexia, aches/pain, fatigue, headache, and/or nausea. No significant organ toxicity was reported. Two patients were treated at the 3×10^9 pfu dose and both patients experienced dose limiting toxicities (DLTs) after a single treatment with Pexa-Vec. The DLTs experienced by these study patients included asymptomatic Grade 3 hyperbilirubinemia (n = 2), and Grade 3 anorexia and right upper quadrant pain (n = 1). Hyperbilirubinemia was apparently due to tumor swelling post-treatment and occlusion of the adjacent bile duct. The maximum-tolerated dose on the study was therefore defined as 1×10^9 pfu. Response and/or stable disease were observed in 9 out of the 10 evaluable patients. Target tumor responses were demonstrated in 8 patients by RECIST criteria and/or Choi criteria. Responding patients had various tumor types, including HCC. In 3 cases positron-emission tomography – computed tomography (PET-CT) scans demonstrated a decrease in injected tumor metabolic activity (10–100% decrease standardized uptake value [SUV]). Eight patients (57%) survived for at least 8 months, and up to 72+ months. The median cancer-specific survival was 9 months.

1.2.2.3.2 Phase 2 Liver Cancer (HCC) Trial (JX594-IT-HEP007)

A Phase 2 randomized dose-finding trial of Pexa-Vec in patients with liver cancer (HCC) (JX594-IT-HEP007) has been completed and the results published[4]. Pexa-Vec was administered by IT injection every 2 weeks for 3 total doses in patients with injectable tumors within the liver. Study dose levels were 1 x 10^8 pfu (Arm A) and 1 x 10^9 pfu (Arm B). Thirty patients were treated (16 patients in Arm A, 14 patients in Arm B). Twenty-nine patients received all 3 planned injections; one low-dose patient received 2 Pexa-Vec treatments. IT injection was well-tolerated at both dose levels in this population of patients with HCC. One treatment-related serious adverse event (SAE) was reported in the high-dose group (nausea and vomiting requiring prolonged hospitalization). Flu-like symptoms (Grade 1–2) occurred in all patients over the first 12–24 hours after treatment, including fever, rigors, nausea or vomiting. Four patients responded to treatment based on mRECIST criteria (1 complete response; 3 partial responses). Responses were observed in injected and non-injected tumors. Further, overall survival was significantly longer in the high-dose arm compared with the low-dose arm (median 14.1 months versus 6.7 months, hazard ratio [HR] 0.39; p-value 0.020, Gehan-Breslow-Wilcoxon test; 1-sided test for superiority of high-dose (**Figure 1**). The median overall survival was 9.0 months for the entire population.

Figure 1: Kaplan-Meier Plot of Overall Survival by Dose



1.2.2.3.3 Phase 2 Study of HCC Patients Treated IV and IT with Pexa-Vec Prior to Sorafenib (JX594-HEP016)

Twenty-five patients were enrolled on this Phase 2 study investigating one IV dose of Pexa-Vec, followed by 2 IT injections (one week and 3 weeks after the IV infusion), prior to initiation of standard sorafenib therapy. Twenty patients were resistant to sorafenib therapy before Pexa-Vec treatment. Transient flu-like symptoms following Pexa-Vec treatments were the most common AEs. Subsequent therapy with sorafenib was well-tolerated. The 2 agents were not used simultaneously, as sorafenib inhibits Pexa-Vec replication and can potentially impair its activity.

Transient decreases in white blood cell (WBC) counts, in particular neutrophils and lymphocytes, may occur within the first 24 hours following each Pexa-Vec treatment dose. Modified Choi

responses and/or disease stabilization were observed following IV and IT Pexa-Vec therapy prior to and following standard sorafenib therapy. One patient exhibited a partial response by RECIST criteria in addition to a response by Choi criteria.

1.2.2.3.4 Phase 2b Randomized Trial of Pexa-Vec Plus Best Supportive Care Versus Best Supportive Care in Patients with Advanced Hepatocellular Carcinoma Who Have Failed Sorafenib Treatment (JX594-HEP018/TRAVERSE)

One hundred and twenty-nine patients having failed previous sorafenib therapy were enrolled on this Phase 2b study and randomized 2:1 to receive either Pexa-Vec plus best supportive care (BSC) or BSC alone. Eighty-six patients were assigned to the Pexa-Vec arm and were to receive one IV dose followed by up to 5 IT injections (1, 3, 6, 12, and 18 weeks after the IV infusion), and 43 to BSC-only arm.

The most common AEs related to Pexa-Vec experienced by patients in Arm A included: pyrexia (78.6%), chills (50.0%), pustular rash (28.6%), hypotension (26.2%), and nausea (25%). These AEs were generally mild-to-moderate in severity and tolerable with the exception of hypotension, which was more severe than previously observed in other trials of Pexa-Vec.

Grade 3 AEs possibly or probably related to Pexa-Vec included pyrexia (8.3%), hypotension (8.3%), blood bilirubin increased (4.8%), anemia (3.6%), blood aspartate transaminase (AST) increased (3.6%); fatigue, hepatic encephalopathy, hypertension, platelet count decreased, vomiting, (2.4% for each event); abdominal pain and blood alanine aminotransferase (ALT) increased (1.2% for each event). Two Grade 4 or Grade 5 events were noted: respiratory failure (Grade 4) and hepatic failure (Grade 5).

Six patients presented with at least one Grade 3–4 AE possibly or probably related to IT injection procedure (7.1%): these AEs included hypotension (2.4%), upper abdominal pain, acute respiratory failure, anemia, ascites, fluid overload, hepatic hemorrhage, pleural effusion, acute renal failure, staphylococcal sepsis, and troponin increase (1.2% for each event). No procedure-related AE resulted in the patient's death.

The most frequent Pexa-Vec-related SAE, which occurred in 6 patients (8 SAEs) was severe hypotension defined as a systolic blood pressure <90 mmHg, lasting and requiring a medical treatment for at least 24 hours after Pexa-Vec administration. Notably, anti-hypertensive medication was ongoing at the time of treatment with Pexa-Vec prior to the development of hypotension in the majority of these patients, thereby possibly exacerbating the potential for hypotension.

Treatment with Pexa-Vec did not improve overall survival or other efficacy measures, compared with BSC, in patients with advanced HCC in this open-label study. No significant improvement of overall survival was shown in Arm A compared to Arm B ($p = 0.426$, stratified log-rank test) for the Intent-to-Treat (ITT) population. Median overall survival was 4.2 (95% confidence interval [CI]: 3.3 to 5.4 months) vs 4.4 months (95% CI: 3.2 to 6.0 months) for Arm A vs Arm B, respectively. HR observed was 1.19 (95% CI: 0.78 to 1.80). The overall disease control rate (proportion of patients with complete response [CR], partial response [PR], or SD) during the study was 13% (95% CI: 7% to 22%) vs 19% (95% CI: 8% to 33%) for Arm A vs Arm B, respectively. Notably, the majority of patients in TRAVERSE did not receive the complete protocol specified treatment regimen of JX-594. In Arm

A, 12 of 86 randomized patients (13.9%) received all 6 planned treatments; and only half of the patients (51.2%) received at least 3 IT treatments (1 IV plus 3 IT) as administered in previous JX-594 HCC trials.

The limited number of patients completing treatment on Arm A in conjunction with the significantly shorter median overall survival (~4.2 vs 4.4 months on Arms A and B, respectively) observed in this study versus studies of other agents for second line HCC (~7–9 months) suggests a relatively more advanced HCC patient population was included in TRAVERSE.

1.2.3 Induction of adaptive immunity

1.2.3.1 Pexa-Vec

The concept of combining oncolytic viruses with immune-modulation – and specifically immune checkpoint inhibition – has two enormous theoretical advantages: tumor selectivity and ability to trigger adaptive immunity. Direct tumor cell lysis, release of soluble tumor antigens, and danger-associated molecular patterns are all thought to help prime and promote tumor-specific immunity[7]. Apart from the direct oncolytic activity, oncolytic viruses such as Pexa-Vec as well as the herpes virus Talimogene laherparepvec (T-VEC) have been shown to mediate tumor cell death via the induction of innate and adaptive immune responses[8].

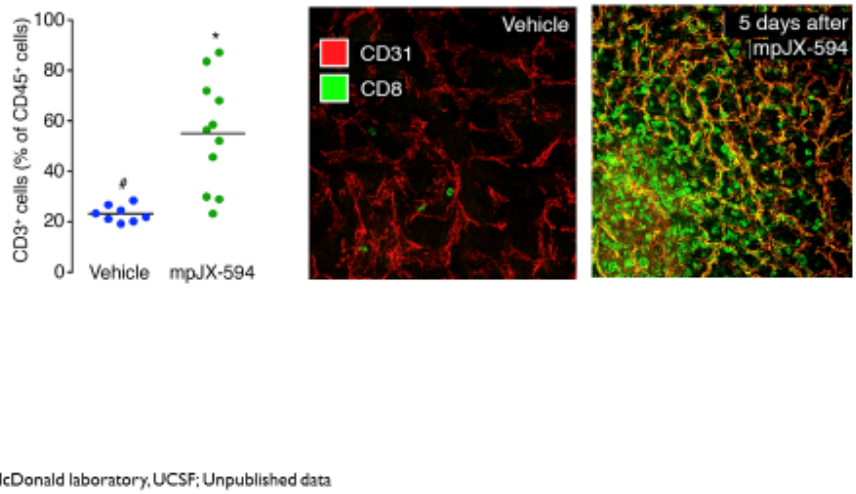
Oncolytic viruses can induce immunogenic cell death and promote an antitumor inflammatory response. A recent preclinical study of Newcastle disease virus (NDV) demonstrated the systemic immune effects that can occur even when virus is injected locally[3]. In a murine model with B16 melanomas established on the bilateral flanks, direct unilateral intratumoral injection of NDV produced significant increases in tumor-specific CD4 and CD8 + T cells in the contralateral (noninjected) tumor. Moreover, the combination of local NDV and systemic CTLA-4 blockade led to significant increases in tumor regression systemically. The most advanced – in terms of clinical development – oncolytic virus is Talimogene laherparepvec (T-VEC) which was approved by the FDA on October 15, 2015 for melanoma. T-VEC is a herpes simplex virus-1-based oncolytic immunotherapy. T-VEC is now being tested in combination with both CTLA-4 and PD-1 blockade. In a phase 1b trial of T-VEC plus ipilimumab, 18 patients unresectable melanoma were enrolled. Treatment was well tolerated (grade 3–4 immune-related adverse events occurred in only two patients) and efficacy was promising (objective response was seen in 56%, and 33% had complete response)[9].

1.2.3.2 Preclinical update

1.2.3.2.1 Evidence of oncolytic vaccinia efficacy and immune activation in a RIP-Tag2 transgenic mouse model of pancreatic cancer

Anti-tumor as well as immune effects following IV oncolytic vaccinia treatment was interrogated in RIP-Tag2 mice, a transgenic model in which mice develop pancreatic neuroendocrine tumors. These tumors are VEGF driven, therefore are also representative of several angiogenic tumors, such as renal cell carcinoma. Experimental models such as this, represent human cancer more accurately than do the commonly used xenograft models -- in which human tumors are transplanted into nude mice. This is because xenografts do not develop in their normal tissue environment, the tumor-stroma interactions that support tumor growth are absent and contributions of adaptive immunity to efficacy cannot be interrogated.

Oncolytic vaccinia injected I.V. into RIP-Tag mice bearing tumors, selectively infects tumors, replicates, and causes tumor cell death by apoptosis. Virus spread can be monitored by anti-vaccinia antibody staining, and tumor cell death by staining for activated caspase-3 in sections of excised tumors. Immunofluorescence based staining of the vasculature (anti-CD31) and lymphocyte infiltrate (CD45), in control and treated tumors, revealed a significant increase in both numbers and distribution of CD45+ leukocytes in vaccinia treated mice. T cell recruitment to tumors was demonstrated 5 days post IV vaccinia administration (**Figure 2**). CD8 T cells recruited to tumors were also shown to be activated (as evidenced by granzyme B positivity, data not shown).



McDonald laboratory, UCSF; Unpublished data

Figure 2: FACS analysis and immunohistofluorescence base staining with anti CD8 anti-bodies

These data support a model in which oncolytic vaccinia virus treatment induces tumor lysis that secondarily leads to infiltration and activation of immune cells in the tumor micro-environment. We then explored whether this immune response could be further activated by combining treatment with vaccinia virus with an immune checkpoint blocking antibody targeting the protein PD-1.

1.2.3.2.2 Combination of oncolytic vaccinia virus with anti-PD-1 antibody in RIP-Tag2 mice

Anti-tumor activity of the combination of oncolytic vaccinia and anti-PD-1 antibody was evaluated in RIP-Tag2 mice by quantification of activated caspase 3 (marker of apoptosis).

As demonstrated in **Figure 3,** while virus alone induced the expected levels of cell death, addition of anti-PD-1 antibody led to significantly enhanced tumor cell death, when used in combination (analysis performed at Day 5 post single agent or combination treatment regimen). No significant effect of the anti-PD-1 antibody alone were seen in this experiment.

These results provide for a rational basis for combining Pexa-Vec and an anti-PD1 antibody in clinical trials of a combination treatment for renal cell carcinoma.

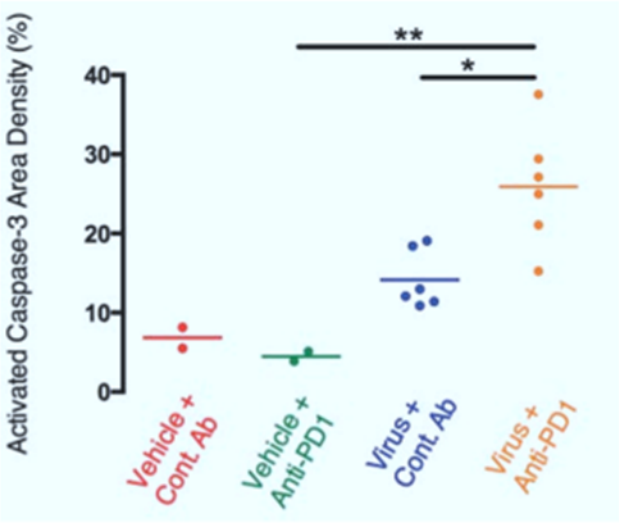


Figure 3. Enhanced tumor cell death induced by combination JX594 and anti-PD-1 treatment as compared with anti-PD-1 alone or oncolytic vaccinia alone

1.3 Tremelimumab

Tremelimumab is a human immunoglobulin (Ig)G2 mAb that is directed against CTLA-4 and is being developed by AstraZeneca for use in the treatment of cancer.

To date tremelimumab has been given to more than 1000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Refer to the current tremelimumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.4 Durvalumab

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1 to PD-1 and CD80 and is being developed by AstraZeneca/MedImmune for use in the treatment of cancer. (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) As durvalumab is an engineered mAb, it does not induce antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. The proposed mechanism of action for durvalumab is interference of the interaction of PD-L1 with PD-1 and CD80.

To date durvalumab has been given to more than 1800 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Refer to the current durvalumab

Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.5 Anti-CTLA4 in combination with anti-PD1/PD-L1

Because the mechanisms of action of CTLA-4 and PD-1 are non-redundant targeting both PD-1 and CTLA-4 pathways may have additive or synergistic activity [10]; therefore, in addition to evaluating both agents in the monotherapy setting in a number of cancer indications AstraZeneca is also investigating the use of durvalumab + tremelimumab combination therapy for the treatment of cancer.

Study D4190C00006 is a Phase Ib dose-escalation study to establish the safety, PK/pharmacodynamics, and preliminary anti-tumor activity of durvalumab + tremelimumab combination therapy in patients with advanced NSCLC. The dosing schedule utilized is durvalumab every 2 or 4 weeks (Q2W, Q4W) up to 12 months, combined with tremelimumab Q4W up to Week 24 for 7 doses then every 12 weeks (Q12W) for 2 additional doses for up to 12 months. The study is ongoing and continues to accrue. In addition, other clinical studies have since started looking at the combination in both NSCLC and other oncology indications.

To date more than 100 patients have received the combination using a number of doses and dosing schedules. Refer to the current editions of the durvalumab and tremelimumab IBs for a complete summary of non-clinical and clinical information including safety, PK and efficacy.

1.5.1 Durvalumab and tremelimumab dose and treatment regimen justification

The durvalumab + tremelimumab combination therapy doses and regimen selected for this study are based on the goal of selecting an optimal combination dose of durvalumab and tremelimumab that would yield sustained target suppression (sPD-L1), demonstrate promising efficacy, and have an acceptable safety profile.

1.5.1.1 Pharmacokinetics/Pharmacodynamics data

Study D4190C00006 included dose cohorts with both a Q4W and a Q2W schedule of durvalumab in combination with a Q4W schedule of tremelimumab. The Q4W schedule was included to align with the Q4W dosing of tremelimumab. PK simulations from durvalumab monotherapy data indicated that a similar area under the plasma drug concentration-time curve at steady state (AUCss; 4 weeks) was expected following both 10 mg/kg Q2W and 20 mg/kg Q4W dosing with durvalumab. The observed durvalumab PK data from the D4190C00006 study were in line with the predicted monotherapy PK data developed pre-clinically and in line with that seen in the first-time-in-human (FTIH), single agent study (CD-ON-MEDI4736-1108) in patients with advanced solid tumors. This demonstrates similar exposure of durvalumab 20 mg/kg Q4W and 10 mg/kg Q2W, with no alterations in PK when durvalumab and tremelimumab (doses ranging from 1 to 3 mg/kg) are dosed together. While the median maximum plasma concentration at steady state (Cmax,ss) is expected to be higher with 20 mg/kg Q4W (approximately 1.5-fold) and median trough concentration at steady state (Ctrough,ss) is expected to be higher with 10 mg/kg Q2W (approximately 1.25-fold), this is not expected to impact the overall safety and efficacy profile, based on existing preclinical and clinical data.

Monotonic increases in pharmacodynamic activity were observed with increasing doses of tremelimumab relative to the activity observed in patients treated with durvalumab monotherapy. There was evidence of augmented pharmacodynamic activity relative to durvalumab monotherapy

with combination doses containing 1 mg/kg tremelimumab, including both the 15 and 20 mg/kg durvalumab plus 1 mg/kg tremelimumab combinations.

Recent updated PK and pharmacodynamic data from regimens that used tremelimumab doses of greater than 1 mg/kg from Study D4190C00006 indicated superior efficacy with combination regimen of durvalumab 1500 mg Q4W plus tremelimumab 300 mg × 1 dose. An approximate dose-proportional increases in PK exposure (maximum serum concentration and area under the serum drug concentration-time curve from time 0 to Day 28 post-dose) was observed with increasing doses of tremelimumab (1, 3, and 10 mg/kg). An exploratory pharmacodynamic analysis bioanalytically evaluated the effects of tremelimumab on proliferating T-cells from NSCLC patients who received tremelimumab (1, 3, or 10 mg/kg) and durvalumab (15 or 20 mg/kg) combination treatment. Monotonic increases in pharmacodynamic activity with the combination (increased activation/ proliferation markers on CD4 and CD8 T-cells in periphery) were observed with increasing doses of tremelimumab (1, 3, 10 mg/kg). The peak increase (%) from baseline of CD4+Ki67+ T-cells was observed 8 days post administration, and the peak level was significantly increased ($p \leq 0.05$) as increasing dose of tremelimumab in the range of 1 to 10 mg/kg. Study data also suggested that higher peak exposure (maximum serum concentration [C_{max}]) of tremelimumab is related to a higher maximum pharmacodynamic effect in the NSCLC patient population. Overall, the PK/pharmacodynamic data suggest that tremelimumab of dose greater than 1 mg/kg with a higher peak exposure may be associated with a higher pharmacodynamic effect.

Additionally, based on simulation data, the C_{max} (78 µg/mL) post single dose administration of tremelimumab 4 mg/kg is approximately 4-fold higher than the predicted C_{max} (19 µg/mL) post the first dose of tremelimumab 1 mg/kg, and is 3-fold higher than the predicted C_{max} (25 µg/mL) post the fourth dose of tremelimumab 1 mg/kg in a Q4W×4 doses setting.

1.5.1.2 Clinical data

In Study D4190C00006 various dose combinations have been explored, with doses of tremelimumab ranging from 1 to 10 mg/kg and doses of durvalumab ranging from 3 to 20 mg/kg. Tremelimumab was given on a Q4W schedule whilst durvalumab was explored in both a Q4W and Q2W schedule, with the goal of identifying the dose combination that best optimizes the risk: benefit profile in an acceptable range of PK and pharmacodynamic values.

Patients treated with doses of tremelimumab above 1 mg/kg had a higher rate of adverse events (AEs), including discontinuations due to AEs, serious AEs (SAEs), and severe AEs. Between the 10 mg/kg durvalumab + 1 mg/kg tremelimumab and 10 mg/kg durvalumab + 3 mg/kg tremelimumab cohorts treated at the Q2W schedule, the number of patients reporting any AE, ≥ Grade 3 AEs, SAEs, and treatment-related AEs was higher in the 10 mg/kg durvalumab + 3 mg/kg tremelimumab cohort than the 10 mg/kg durvalumab + 1 mg/kg tremelimumab cohort. A similar pattern was noted in the Q4W regimens, suggesting that, as the dose of tremelimumab increased above 1 mg/kg, a higher rate of treatment-related events may be anticipated. Further, the SAEs frequently attributed to immunotherapy, pneumonitis, colitis and other immune mediated events, were more commonly seen in cohorts using either 3 mg/kg or 10 mg/kg of tremelimumab compared to the 1-mg/kg dose cohorts. Together, these data suggest that a combination using a tremelimumab dose of 1 mg/kg appeared to minimize the rate of toxicity when combined with durvalumab. As a result, all combination doses utilizing either the 3 or 10-mg/kg doses of tremelimumab were eliminated in the final dose selection.

In contrast, cohorts assessing higher doses of durvalumab with a constant dose of tremelimumab did not show an increase in the rate of AEs. The data suggested that increasing doses of durvalumab may not impact the safety of the combination as much as the tremelimumab dose. Further, safety data between the 10-mg/kg and 20-mg/kg cohorts were similar, with no change in safety events with increasing dose of durvalumab.

In Study D4190C00006, of all treatment cohorts, the cohort of patients treated in the 20 mg/kg durvalumab + 1 mg/kg tremelimumab group had a tolerable safety profile, but still showed strong evidence of clinical activity. No dose-limiting toxicities (DLTs) were reported in this cohort.

Preliminary clinical activity of the durvalumab and tremelimumab combination did not appear to change with increasing doses of tremelimumab. The 15- and 20-mg/kg durvalumab Q4W cohorts demonstrated objective responses at all doses of tremelimumab, and increasing doses of tremelimumab did not provide deeper or more rapid responses.

Efficacy data suggested that the 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose cohort may demonstrate equivalent clinical activity to other dose combinations. Of the 14 patients in this cohort, there were 4 patients (29%) with PR, 4 patients (29%) with SD, and 2 patients (14%) with PD. Two patients were not evaluable for response.

A single dose of tremelimumab 4 mg/kg, while maintaining a similar overall exposure, has a 3- to 4-fold higher C_{max} compared to the 4 doses of tremelimumab 1 mg/kg. Therefore, this single administration of the higher dose of tremelimumab may have the potential for better anti-tumor activity while potentially avoiding any cumulative toxicity associated with repeated dosing of the 1 mg/kg tremelimumab.

In the Phase I/II study (Study D4190C00022) evaluating the tolerability and clinical activity of durvalumab and tremelimumab in advanced HCC patients who progressed on, are intolerant of, or refused sorafenib-based therapy, durvalumab (1500 mg Q4W) as a single agent and in combination with two dosing regimens of tremelimumab (75 mg Q4W X 4 doses or 300mg X 1 dose) were evaluated. In the pre-planned interim analysis, safety data showed that both combination dose regimens were tolerable and no new safety signals were identified. While efficacy for durvalumab in combination with tremelimumab at the 75mg dose (Q4W X 4) was not meaningfully better than durvalumab monotherapy, efficacy data supports continued evaluation of durvalumab in combination with tremelimumab at the 300mg dose (X1). Therefore, durvalumab in combination with tremelimumab 300 mg x 1 dose will only be continued evaluation in the phase I/II study (Study D4190C00022) and Phase III study (Study D419CC00002).

Altogether, the data suggested that a 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose combination should be selected for further development.

Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information on the durvalumab + tremelimumab combination, including safety, efficacy and pharmacokinetics.

1.5.1.3 Rationale for 4 cycles of combination therapy followed by durvalumab monotherapy

Long -term follow up on melanoma patients treated with ipilimumab, an anti-CTLA-4 targeting antibody (dosed every 3 weeks [Q3W] for 4 doses and then discontinued), shows that patients responding to ipilimumab derive long-term benefit, with a 3-year OS rate of approximately 22%. Furthermore, the survival curve in this population reached a plateau at 3 years and was maintained through 10 years of follow up.

Similar data have been presented for other anti-PD-1/PD-L1 targeting antibodies:

Nivolumab (anti-PD-1) was dosed Q2W for up to 96 weeks in a large Phase I dose escalation and expansion study, and showed responses were maintained for a median of 22.94 months for melanoma (doses 0.1 mg/kg to 10 mg/kg), 17 months for NSCLC (doses 1, 3, and 10 mg/kg), and 12.9 months for renal cell carcinoma patients (doses 1 and 10 mg/kg) at the time of data analysis[11]. Furthermore, responses were maintained beyond treatment discontinuation in the majority of patients who stopped nivolumab treatment (either due to protocol specified end of treatment, CR, or toxicity) for up to 56 weeks at the time of data analysis.

Similar long-term results may be expected with use of other immune-mediated cancer therapeutics such as tremelimumab, durvalumab, or the combination of the two agents.

The durvalumab + tremelimumab combination regimen will be administered for 4 doses Q4W followed by durvalumab monotherapy Q4W for up to a maximum of 2 years' total.

1.5.2 Durvalumab monotherapy dose rationale

A durvalumab dose of 20 mg/kg Q4W is supported by in vitro data, non-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study 1108 in patients with advanced solid tumors and from a Phase I trial performed in Japanese patients with advanced solid tumor (D4190C00002).

1.5.2.1 PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W, durvalumab exhibited non-linear (dose dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg Q2W, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg Q2W is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab (For further information on immunogenicity, please see the current IB).

Data from Study D4190C00006 (Phase I trial in NSCLC patients using the combination of durvalumab and tremelimumab) also show an approximately dose-proportional increase in PK exposure for durvalumab over the dose range of 3 to 20 mg/kg durvalumab Q4W or Q2W. (For further information on PK observations in Study 006, please see the current IB).

The observed durvalumab PK data from the combination study were well in line with the predicted monotherapy PK data (5th median and 95th percentiles) for a Q4W regimen.

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W (Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q2W and 20 mg/kg Q4W regimens, as represented by AUCss (4 weeks). Median Cmax,ss is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median Ctrough,ss is expected to be higher with 10 mg/kg Q2W (~1.25 fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q2W with the proposed similar dose of 20 mg/kg Q4W expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical

activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar area under the plasma drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD L1 suppression at trough, and the available clinical data, the 20 mg/kg Q4W and 10 mg/kg Q2W regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg Q4W.

1.5.3 Fixed Dosing for durvalumab and tremelimumab

A population PK model was developed for durvalumab using monotherapy data from a Phase 1 study (study 1108; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight (WT) on PK of durvalumab (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen.

Similarly, a population PK model was developed for tremelimumab using data from Phase 1 through Phase 3 (N=654; doses= 0.01 to 15 mg/kg Q4W or Q90D; metastatic melanoma) [12]. Population PK model indicated minor impact of body WT on PK of tremelimumab (coefficient of ≤ 0.5). The WT-based (1 mg/kg Q4W) and fixed dosing (75 mg/kg Q4W; based on median body WT of ~75 kg) regimens were compared using predicted PK concentrations (5th, median and 95th percentiles) using population PK model in a simulated population of 1000 patients with body weight distribution of 40 to 120 kg. Similar to durvalumab, simulations indicated that both body WT-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-subject variability with fixed dosing regimen.

Similar findings have been reported by others [13][, [14], [15], [16]. Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies. In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in pharmacokinetic/pharmacodynamics parameters [15].

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 750 mg Q2W MEDI4736 (equivalent to 10 mg/kg Q2W), 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) and 75 mg Q4W tremelimumab (equivalent to 1 mg/kg Q4W) is included in the current study.

Fixed dosing of durvalumab and tremelimumab is recommended only for subjects with > 30kg body weight due to endotoxin exposure. Patients with a body weight less than or equal to 30 kg are not eligible for enrollment in the current study, and if a patient's body weight drops below 30

kg while on the study, the patient should be dosed using a weight-based dosing schedule as long as their body weight remains < 30 kg.

For patients treated with tremelimumab in the current study, subjects must have a body weight of > 35 kg to enroll and they will be treated with a fixed dose of tremelimumab. If a patient's body weight drops below 33 kg while on the study, the patient should be dosed with tremelimumab using a weight-based dosing schedule for as long as their body weight remains < 33 kg and according to the study protocol.

1.6 Rationale for timing and mandatory nature of the biopsies

Whilst the preclinical data suggest induction of immune cell infiltration following oncolytic viral therapy, with potential for amplification with immune checkpoint therapy, the effect in colorectal cancer – a relatively non-immunogenic tumor – is really unknown. Given that this is essentially a small pilot study evaluating feasibility and safety whose next step in development – if safe and feasible – will most likely be a larger randomized study, it is scientifically important to obtain as much information about the treatment effect. This may lead to altered and improved design of the next study. The best strategy for doing this is with tumor biopsies in order to evaluate immune cell infiltration (CD4/8 T-cells, MDSC). However, if a patient has technically biopsiable disease but the interventional radiologist has concerns that pursuing the biopsy increases the risk to above average, or if pursuing the biopsy creates additional logistical complications (availability, pre-anesthesia requirements etc.) which cause delays or inconvenience to an unreasonable degree, we will forgo at investigator discretion. The timing of the biopsies reflects twin aims of evaluating immune infiltration post-virus and also post-combination therapy. The baseline –day 1 paired biopsies will provide data on the immune impact of the virus (within the TME) and the baseline – day 29 paired samples will provide data on the immune impact of the combination of the vaccine and immune checkpoint inhibitor. Given the difficulty in obtaining three separate tumor biopsies we have elected to perform a baseline on all patients and then either the D1 or D29 biopsy.

1.7 Amendment D Rationale

Considering recent updated PK and pharmacodynamic data from regimens that used tremelimumab (Section **1.5.1.1**) and clinical benefit of increased single tremelimumab dose (Section **1.5.1.2**) with Amendment D we change study design and replace 4 infusions (75 mg each) of tremelimumab with single infusion (300 mg).

We completed enrollment into Arms A1 and A2 and with approval of this amendment we are proceeding to enrollment to Arms B1 and B2 with addition of tremelimumab to combined treatment.

Overall, combination of Pexa-Vec with durvalumab even on dose level 2 of Pexa-Vec showed favorable safety profile. No DLT was developed. All patients who received the treatment tolerated well. There were no drug-related discontinuations or deaths. Drug-related AEs occurred in 100% of patients and were grade 3-4 in 8.6%. See (**Appendix D)**

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 Eligibility Criteria

2.1.1 Inclusion Criteria

2.1.1.1 Patients must have histopathological confirmation of Colorectal Carcinoma (CRC) by the Laboratory of Pathology of the NCI prior to entering this study.

2.1.1.2 Patients must have progressed on, been intolerant of or refused prior oxaliplatin- and irinotecan-containing, fluorouracil-based, chemotherapeutic regimen and have disease that is not amenable to potentially curative resection. Patients who have a known KRAS wild type tumor must have progressed, been intolerant of or refused cetuximab or panitumumab-based chemotherapy.

2.1.1.3 Patients tumors must be documented to be microsatellite-stable (MSS) either by genetic analysis or immunohistochemistry OR microsatellite-high with documented disease progression following anti-PD1/PDL1 therapy.

2.1.1.4 Patients must have at least one focus of metastatic disease that is amenable to pre- and on-treatment biopsy and be willing to undergo this. Ideally the biopsied lesion should not be one of the target measurable lesions, although this can be up to the discretion of the investigators.

2.1.1.5 All patients enrolled will be required to have measurable disease by RECIST 1.1 criteria.

2.1.1.6 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of Pexa-Vec in combination with tremelimumab and/or durvalumab in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

2.1.1.7 ECOG performance status 0-1 (see **Appendix A**)

2.1.1.8 Patients must have acceptable organ and marrow function as defined below:

Leukocytes	≥3,000/mcL
absolute neutrophil count	≥ 1,500/mcL
Platelets	≥100,000/mcL
total bilirubin	≤1.5X institution upper limit of normal
Hb	> 9g/dl
AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 5x ULN	
Creatinine	<1.5X institution upper limit of normal
	OR

creatinine clearance	≥45 mL/min/1.73 m^2, as calculated below, for patients with creatinine levels above institutional normal

Estimated creatinine clearance (mL/min)

$$\text{Females} = \frac{140 - (\text{pt's age [y]}) \times \text{body weight [kg]}}{72(\text{serum creatinine [mg/dL]})} \times 0.85 \times \frac{1.73\ m^2}{(\text{pt's BSA } [m^2])}$$

$$\text{Males} = \frac{140 - (\text{pt's age [y]}) \times \text{body weight [kg]}}{72(\text{serum creatinine [mg/dL]})} \times \frac{1.73\ m^2}{(\text{pt's BSA } [m^2])}$$

May use a 24-hr. urine collection to determine creatinine clearance.

Measured creatinine clearance (mL/min)

$$\frac{(\text{urine creatinine [mg/dL]}) \times (\text{urine volume [mL]})}{(\text{serum creatinine [mg/dL]}) \times (1440\ \text{min})} \times \frac{1.73\ m^2}{(\text{pt's BSA } [m^2])}$$

2.1.1.9 Patient must be able to understand and willing to sign a written informed consent document

2.1.1.10 The effects of Pexa-Vec, durvalumab and tremelimumab on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation and up to 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period. 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.

2.1.1.11 Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy. Subject is willing and able to comply with the protocol for the

duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

2.1.1.12 Body weight >35kg

2.1.2 Exclusion Criteria

2.1.2.1 Patients who have had anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies or other investigation agents), large field radiotherapy, or major surgery must wait 4 weeks after completing treatment prior to entering the study.

2.1.2.2 No prior exposure to immune-mediated therapy including, but not limited to, other anti CTLA-4, anti-PD-1, anti-PD-L1, and anti-programmed cell death ligand 2 (anti-PD-L2) antibodies, including therapeutic anticancer vaccines. The exception to this is those whose tumors are MSI-hi and are refractory to anti-PD1 monotherapy.

2.1.2.3 Involvement in the planning and/or conduct of the study

2.1.2.4 Previous IP assignment in the present study

2.1.2.5 Patients who are receiving any other investigational agents.

2.1.2.6 Inability to suspend treatment with anti-hypertensive medication (including but not limited to: diuretics, beta-blockers, angiotensin converting enzyme [ACE] inhibitors, aldosterone antagonists, etc.) for 48 hours pre and post each Pexa-Vec administration.

2.1.2.7 Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria

2.1.2.8 Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis

2.1.2.9 Patients with known brain metastases will be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

2.1.2.10 Uncontrolled intercurrent illness including, but not limited to, hypertension (systolic BP > 160, diastolic BP > 100), ongoing or active systemic infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, uncontrolled diabetes or psychiatric illness/social situations that would limit compliance with study requirements. For patients with a history of cardiovascular disease, cardiology consultation is required. Echocardiogram, troponin and creatinine clearance must be obtained prior to enrollment. NOTE: Patients with active cardiac disease (e.g. myocarditis and myocardial infarction) within 12 months of study entry are excluded from study participation.

2.1.2.11 HIV-positive patients receiving anti-retroviral therapy are excluded from this study due to the possibility of pharmacokinetic interactions between antiretroviral medications and the investigational agent. HIV positive patients not receiving antiretroviral therapy are excluded due to the possibility that Durvalumab or Tremelimumab may worsen their

condition and the likelihood that the underlying condition may obscure the attribution of adverse events.

2.1.2.12 Known significant immunodeficiency due to underlying illness (e.g. HIV/AIDS) and/or immune-suppressive medication including high-dose corticosteroids (defined as ≥20 mg/day prednisone or equivalent which is ongoing at the time of enrollment and/or was taken for more than 4 weeks within the preceding 2 months of enrollment)

2.1.2.13 History of chronic autoimmune disease (e.g. systemic lupus erythematosus or Wegener's granulomatosis, Addison's disease, multiple sclerosis, Graves' disease, Hashimoto's thyroiditis, hypophysitis, etc.) with symptomatic disease within the 3 years before enrollment. Note: Active vitiligo or a history of vitiligo will not be a basis for exclusion. In addition, a past history of certain autoimmunity e.g. rheumatoid arthritis or thyroiditis may be allowed per PI discretion provided it has been quiescent for a minimum of three years. The following are exceptions to this criterion:

a) Patients with vitiligo or alopecia

b) Patients with hypothyroidism (e.g. following Hashimoto syndrome) stable on hormone replacement

c) Any chronic skin condition that does not require systemic therapy

d) Patients without active disease in the last 5 years may be included

e) Patients with celiac disease controlled by diet alone

f) Active or history of inflammatory bowel disease (colitis, Crohn's), irritable bowel disease, celiac disease, or other serious, chronic, gastrointestinal conditions associated with diarrhea.

2.1.2.14 History of active primary immunodeficiency

2.1.2.15 Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing (if clinically indicated), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

2.1.2.16 Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. The following are exceptions to this criterion:

- Intranasal, inhaled, topical steroids, or local steroid injections (e.g. intra articular injection)
- Systemic corticosteroids at physiologic doses not to exceed <<10 mg/day>> of prednisone or its equivalent
- Steroids as premedication for hypersensitivity reactions (e.g. CT scan premedication)
- Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.

2.1.2.17 Female patients who are breastfeeding. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with Pexa-Vec,

breastfeeding should be discontinued if the mother is treated with Pexa-Vec. These potential risks may also apply to other agents used in this study.

2.1.2.18 Known allergy or hypersensitivity to IP

2.1.2.19 Prior randomization or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment.

2.1.2.20 History of sarcoidosis syndrome

2.1.2.21 Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fredericia's Correction

2.1.2.22 Patients with a history of Interstitial lung disease or pneumonitis

2.1.2.23 Subjects with uncontrolled seizures

2.1.2.24 History of leptomeningeal carcinomatosis

2.1.2.25 History of hypersensitivity reaction to human or mouse antibody products.

2.1.2.26 Patients with unhealed surgical wounds for more than 30 days

2.1.2.27 Ongoing severe inflammatory skin condition (as determined by the Investigator) requiring medical treatment

2.1.2.28 History of severe eczema (as determined by the Investigator) requiring medical treatment

2.1.2.29 Patients with tumor(s) invading a major vascular structure (e.g. carotid artery) or other key anatomical structure (e.g. pulmonary airway) in the event of post treatment tumor swelling and/or necrosis (hepatic and portal vein involvement allowed)

2.1.2.30 Patients with liver tumors in a location that would potentially result in significant clinical adverse effects in the opinion of investigator if post-treatment tumor swelling were to occur, including at the site of the common bile duct

2.1.2.31 Clinically significant and/or rapidly accumulating ascites, pericardial and/or pleural effusions. Mild ascites that does not preclude safe tumor biopsy as protocol specified is allowed at the discretion of the treating physician.

2.1.2.32 Medical conditions, per the investigator's judgment, that predispose the patient to untoward medical risk in the event of volume loading (e.g. intravenous [IV] fluid bolus infusion), tachycardia, or hypotension during or following treatment with Pexa-Vec

2.1.2.33 Any prior or planned organ transplant (e.g. liver transplant)

2.1.2.34 Patients who experienced a severe systemic reaction or side-effect as a result of a previous vaccination with vaccinia

2.1.2.35 Pulse oximetry O2 saturation <90% at rest on room air

2.1.3 Recruitment Strategies

The study may be abstracted into a plain language announcement posted on NIH websites and on NIH social media platforms.

2.2 Screening Evaluation

2.2.1 Screening activities performed after a consent for screening has been signed

Screening evaluation testing/procedures are conducted under the separate screening protocol, 01-C-0129 (Eligibility Screening and Tissue Procurement for the NIH Intramural Research Program Clinical Protocols). Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a patient has signed the consent.

Studies should be done within 28 days prior to enrollment unless otherwise noted below.

- History and Physical Evaluation

Complete medical history and physical examination (including height, weight, vital signs, ECG, and ECOG performance status) will be conducted prior to enrollment.

- Laboratory Evaluation
  - Hematological Profile: CBC with differential and platelet count.
  - Biochemical Profile: electrolytes, BUN, creatinine, AST, ALT, total and direct bilirubin, calcium, phosphorus, albumin, magnesium.
  - 24-hour urine collection (if creatinine clearance is measured in this manner)
  - Serum or urine pregnancy test for female participants of childbearing age and anatomic ability.
  - HIV, Hepatitis B and C serology and/or viral load
  - TB testing (if clinically indicated)
- Cardiology Consultation for patients with history of cardiovascular disease (see criterion **2.1.2.10**)
- Echocardiogram
- CT scan of chest, abdomen and pelvis (or MRI of abdomen if clinically indicated)
- Histologic confirmation (at any time point prior to enrollment). If there is no available tumor sample, biopsy will be performed to confirm the diagnosis and Microsatellite Stability Status.
  - A block or unstained slides of primary or metastatic tumor tissue will be required from each participant to confirm diagnosis with analysis being performed by the Laboratory of Pathology, NIH.
  - Documentation of microsatellite status (by PCR or IHC for MMR proteins, at any time point prior to enrollment).

2.3 Participant Registration and Status Update Procedures

Registration and status updates (e.g. when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found here..

2.4 Treatment Assignment Procedures (for registration purposes only):

Cohorts

Number	Name	Description
1	A1	Subjects enrolled to Pexa-Vec escalation dose levels + Durvalumab
2	A2	Subjects enrolled at the MTD of Pexa-Vec after the MTD is established + Durvalumab
3	B1	Subjects enrolled to Pexa-Vec escalation dose levels + Durvalumab + Tremelimumab
4	B2	Subjects enrolled at the MTD of Pexa-Vec after the MTD is established+ Durvalumab + Tremelimumab

Arms

Number	Name	Description
1	A1	Pexa-Vec escalation dose levels + Durvalumab
2	A2	MTD of Pexa-Vec after the MTD is established + Durvalumab
3	B1	Pexa-Vec escalation dose levels + Durvalumab + Tremelimumab
4	B2	MTD of Pexa-Vec after the MTD is established+ Durvalumab + Tremelimumab

Arm assignments

Subjects in cohort A1 will be directly assigned to arm A1.

Subjects in cohort A2 will be directly assigned to arm A2 after the MTD for Arm A1 has been determined.

Subjects in cohort B1 will be directly assigned to arm B1 once enrollment in Arms A1 and A2 are complete.

Subjects in cohort B2 will be directly assigned to arm B2 after the MTD for Arm B1 has been determined.

2.5 Baseline Evaluation

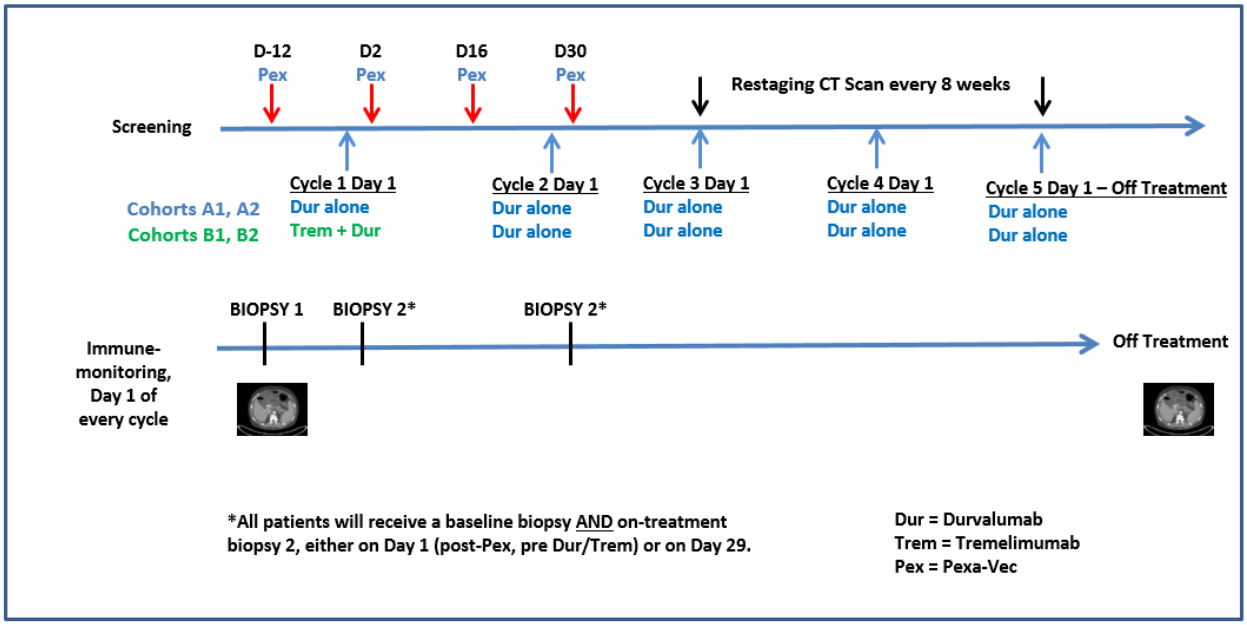
Tests performed during screening do not need to be repeated if done in designated time frame.

- Physical exam with vital signs and ECOG performance status (obtained within 1 week prior to first dose of Pexa-Vec).
- CT scan of chest, abdomen and pelvis (or MRI of abdomen if clinically indicated) (obtained within 28 days prior to first dose of Pexa-Vec)
- Laboratory evaluation (obtained within 72 hours prior to first dose of Pexa-Vec):
  - Hematological profile: CBC with differential and platelet count
  - PT, INR, aPTT, fibrinogen.
  - Biochemical profile: electrolytes, BUN, creatinine, AST, ALT, total and direct bilirubin, calcium, phosphorus, albumin, magnesium, uric acid, amylase and lipase
  - Tumor marker profile: CEA
  - Serum or urine pregnancy test for female participants of childbearing age and anatomic ability.
  - Urinalysis
  - Troponins
- Laboratory evaluation (obtained within 28 days prior to first dose of Pexa-Vec):
  - Thyroid function tests (TSH, T3, T4)
  - ACTH, morning cortisol.
  - HLA subtype
- Electrocardiogram (obtained within 72 hrs. prior to first dose of Pexa-Vec)

3 STUDY IMPLEMENTATION

3.1 Study Design

The proposed study is a Phase I/II study of Pexa-Vec oncolytic virus at two dose levels in combination with immune checkpoint inhibition in patients with metastatic colorectal cancer.



- Patients with advanced microsatellite-stable colorectal cancer (or MSI-hi disease that is refractory to PD-1 monotherapy) will receive Pexa-Vec, administered IV at a dose of either 3 x 10^8 plaque forming units (pfu) (DL1) or 10^9 pfu (DL2) every 2 weeks for 4 doses, in 4 separate arms: A1, A2, B1 and B2. The first administration will be on Day –(minus) 12, followed by administration on Days 2, 16 and 30 (i.e. 4 doses in total).
  - There will be 4 arms, as summarized in **Table 1**: in Arms A1 and A2 subjects will be treated with Pexa-Vec in combination with Durvalumab and in Arms B1 and B2 subjects will be treated with Pexa-Vec in combination with Durvalumab and Tremelimumab. After enrollment is completed for Arms A1 and A2 and full assessment of safety performed, we will report this data to the NIH Intramural IRB. We will only proceed to Arm B1 (Pexa-Vec + Durvalumab + Tremelimumab) upon NIH Intramural IRB approval of updated safety information of ongoing combination therapy evaluating Arms A1 and A2 (Pexa-Vec in combination with Durvalumab).

		Tremelimumab	**Durvalumab**	**Pexa-Vec/pfu**	**N**
Arm A1	DL 1	NA	1500mg q 28d	3 x 10^8	3-6
	DL 2	NA	1500mg q 28d	10^9	6
Arm A2		NA	1500mg q 28d	10^9 (MTD)	4

Arm B1	DL 1	300 mg x 1 at cycle 1	1500mg q 28d	3×10^8	3-6
	DL 2	300 mg x 1 at cycle 1	1500mg q 28d	10^9	6
Arm B2		300 mg x 1 at cycle 1	1500mg q 28d	10^9 (MTD)	4

Table 1**: Arms/Dose levels**

- Enrollment of the first two patients in each dose level will be staggered by 2 weeks in order to observe and treat any unexpected toxicities.

- If 0/3 patients encounter DLT at DL1 we will proceed to DL2, or if 1/3 patients at Dose Level 1 encounter DLT we will expand DL1 to 6 patients as per standard 3+3 criteria. 1/6 with DLT at DL1 will lead to enrollment onto DL2. If 2 or more of 6 patients have a DLT at Dose Level 1, then we will not proceed with further enrollment or will need to revise the treatment regimen before use in a subsequent study, as appropriate.
- If only 1/6 patients at Dose Level 2 encounter DLT we will expand DL2 to 10 patients. If 2 or more of 6 patients have a DLT at Dose Level 2, then we will not proceed with further enrollment and will need to revise the treatment regimen before use in a subsequent study, as appropriate.
    - Arms A1 and A2: In addition to the oncolytic virus patients will also receive durvalumab at a flat dose of 1500mg as an intravenous infusion beginning on Day 1 followed by q28days until off-treatment criteria are met.
    - Arms B1 and B2: In addition to the oncolytic virus patients will also receive tremelimumab 300 mg and durvalumab 1500mg as intravenous infusions on Day 1 followed by q28days subsequent continuation of the durvalumab alone until off-treatment criteria are met.
    - Pexa-Vec will commence on Day –(minus) 12 to facilitate tumor biopsies following oncolytic virus alone.
    - All patients will undergo a baseline tumor biopsy and a post treatment biopsy. Patients will be assigned to receive the second biopsy on Day 1 (i.e. after one dose of Pexa-Vec alone) or Day 29 (i.e. after the combination of immune checkpoint inhibition and Pexa-Vec). (Specific dates of biopsy will have a window of 72 hrs to allow for logistical issues; however, the biopsy will not be performed within 48 hrs after Pexa-Vec administration). Patients should withhold antihypertensive medication for 48 hours pre and post Pexa-Vec administration. Assignment on a 1:1 basis will be performed to determine timing of the second research biopsy. Research Team will assign patient #1 to early second biopsy, patient #2 to late second biopsy and so on.

3.1.1 Dose Limiting Toxicity (DLT)

A DLT is defined as any of the below listed laboratory abnormality or adverse drug reaction (ADR) according to the NCI-CTCAE v 4.3, that is possibly, probably, or definitely related to the combination of Pexa-Vec oncolytic virus with either durvalumab or the combination of durvalumab and tremelimumab, occurring during the DLT evaluation period unless specified as exceptions. ADRs are defined in this trial as any AEs suspected to be related to study treatment by the investigator. The DLT observation period comprises the first 28 days of combination treatment, extending from Day 1 to Day 28, however if later toxicities arise these may also be used to inform DLT determination based on the opinion of the investigator. Eligible patients for DLT evaluation will be those who completed the DLT period and have received at least 60% of the scheduled doses of Pexa-Vec and at least 1 dose of immune checkpoint blockade, or those who discontinue study treatment early due to a DLT. Subjects who are not fully eligible for DLT evaluation will be replaced.

3.1.1.1 Immune-mediated adverse events (imAEs)

- Any Grade 4 imAE not attributed to local tumor response (e.g. inflammatory reaction attributed to local tumor response or inflammatory reaction at sites of metastatic disease or lymph nodes).
- Any Grade ≥3 colitis.
- Any Grade 3 or 4 noninfectious pneumonitis, irrespective of duration or Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care.
- Any Grade 3 imAE, excluding colitis or pneumonitis, that does not downgrade to Grade ≤1 or baseline status (for patients who entered the study with an existing laboratory abnormality) within 14 days.
- Any > grade 2 cardiac toxicity which does not resolve to grade 1 within 3 days of initiation of maximum supportive care.

3.1.1.2 Non-Immune-mediated Adverse Event (Non-imAE)

- Any Grade ≥3 non-imAE toxicity that does not downgrade to Grade ≤1 or baseline status (for patients who entered the study with an existing laboratory abnormality) within 14 days

3.1.1.3 Exclusions to Dose Limiting Toxicities

- Grade 3/4 infusion-related reactions including fever, chills lasting less than 72 hours or hypotension responsive to IVF or other medical therapy (e.g. vasopressors) and resolving in < 24 hrs.
- Vitiligo, alopecia, rash, and Grade 3 electrolyte abnormalities that are reversed with appropriate medical intervention within 7 days or derived from a suboptimal prophylactic and curative therapy
- Grade 4 electrolyte abnormalities lasting less than 72 hours or are clinically irrelevant.
- Grade 3 and 4 diarrhea lasting less than 72 hours.
- Grade 3 fatigue.
- Grade 3 rise in creatinine, not corrected to Grade 1 or less after 2 liters or more of intravenous fluids within 24 hours, will be considered dose limiting.

- Laboratory values out of normal range that are unlikely related to trial treatment according to the investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management.
- Transient (<7days) Grade 3 / 4 fatigue, local reactions, headache, nausea, emesis that resolves to ≤ Grade 1.
- Grade 3 endocrinopathy that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the following criteria are met:
    - The subject's hormone levels are within normal limits
    - The subject is asymptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (e.g. inflammatory reaction at sites of metastatic disease, lymph nodes, etc.). imAEs are defined as AEs of an immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. In the absence of a clinically significant abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT. Laboratory abnormalities that are not deemed to be clinical significant will not be considered a DLT.

3.1.2 Maximum tolerated dose (MTD)

MTD will be that dose where no greater than 1 of 6 patients have a DLT.

3.1.3 Protocol Stopping Rules

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.3 for grading systemic toxicity. For safety reasons, the protocol will be temporarily halted pending discussions with the NIH Intramural IRB and Sponsor regarding necessary amendment for either of the following events:

• One occurrence of grade 5 toxicity by the NCI-CTCAE version 4.3 attributable to the treatment regimen.

• Two occurrences of grade 4 toxicity by the NCI-CTCAE version 4.3 attributable to the treatment regimen.

3.2 Drug Administration

3.2.1 Pexa-Vec Drug Administration

The Pexa-Vec dose of 3 x 10^8 pfu (DL 1) or 1 x 10^9 pfu (DL 2) will be administered via IV infusion over 60 minutes (±5 minutes). Patients will receive 1 L 0.9% Sodium Chloride (NaCl) prior to infusion. Treatments 2–4 may each be administered in a treatment window of ±72hrs. If a treatment is not given within the ±72hrs window, it will be considered missed (e.g. patient will not receive the treatment, but future treatments will be administered as originally outlined in the protocol).

3.2.1.1 Pre-Medication for Treatment Day

To mitigate risk of hypotension following Pexa-Vec treatment, the following are required:

- Prehydration with 1 liter of solute-containing fluid (PO or IV) prior to each treatment

- Suspension of anti-hypertensive medication (including diuretics, beta-blockers, ACE inhibitors, aldosterone antagonists, etc.) for 48 hours prior to and 48 hours after each Pexa-Vec injection.

All patients should be pre-medicated with acetaminophen (or equivalent, unless contraindicated) on each treatment day. For acetaminophen, the following regimen may be used:

- 500–1000 mg 2 hours' pre-infusion
- 500–1000 mg at 4 hours' post-procedure
- 500–1000 mg every 6 hours thereafter, as needed (the total acetaminophen dose should be carefully assessed to avoid cumulative toxicity)

3.2.2 Durvalumab Administration

A dose of 1500mg will be administered as an IV infusion over approximately 60 minutes (±5 minutes).

For details, please, see Section **13.2.5**

Less than 55 minutes is considered a deviation.

If there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

3.2.3 Tremelimumab Administration

A dose of 300 mg will be administered as an IV solution at a rate of 250 mL/hr. Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

For details, please, see Section **13.1.5**

3.2.4 Monitoring of Dose Administration

Pexa-Vec

A 20-hour observation period is required after the first infusion of Pexa-Vec. Vital signs will be collected before infusion, at least once during the infusion, at the completion of the infusion and every 2 hours approximately until completion of 20-hour observation period. At the discretion of the treating physician patients may be admitted for additional supportive care and observation after the 20-hour period. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 8 hours after Pexa-Vec infusion).

Tremelimumab and Durvalumab

Vital signs will be collected before investigational product infusion and at the completion of the infusion. A 1-hour observation period is required after the first infusion of durvalumab and tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab infusion).

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤Grade 2 infusion related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g. diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion related reaction is ≥Grade 3 or higher in severity, study drug will be discontinued. The standard infusion time is one hour, however, if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 8 hours at room temperature (otherwise requires new infusion preparation).

As with any antibody, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis, as per local institutional guidelines.

3.3 Dose Modifications

The following broad guidelines for dose delivery schedule delays and alternations apply to the planned dosages of Pexa-Vec, Tremelimumab and Durvalumab or Durvalumab monotherapy and are dependent on the clinical and laboratory assessment on the day of dosing. Pexa-Vec, Tremelimumab and Durvalumab can be delivered within 72 hours of planned interval to accommodate scheduling issues/logistics.

3.3.1 Pexa-Vec

If a treatment is not given within the ±72-hour window, it will be considered missed (e.g. patient will not receive the treatment, but future treatments will be administered as originally outlined in the protocol).

3.3.2 Tremelimumab and durvalumab

Dose modifications of Durvalumab and tremelimumab may be required in the event of treatment-related toxicity. General guidelines regarding dose modification are provided in **Appendix B**.

3.4 Management of Expected Adverse Events and Events of Special Interest

3.4.1 Expected Toxicities of Pexa-Vec Treatment

3.4.1.1 Flu-Like Symptoms (mild-to-severe fever, rigors, anorexia, aches/pain, fatigue, headache, and/or nausea)

These flu-like symptoms typically peak during the first 12 hours after Pexa-Vec treatment. Acute, fever is expected within 4–12 hours post-treatment and has a typical duration of 18–24 hours, although these can last up to 72 hours.

3.4.1.2 Hypotension

Across clinical trials and indications, mild-to-moderate transient hypotension can be observed within 24 hours following treatment with Pexa-Vec. However, in the TRAVERSE trial for patients with advanced 2nd line HCC, 6 patients (8 total SAEs) have experienced severe hypotension following Pexa-Vec treatment, requiring >24 hours of medical treatment, intensive care unit care, and vasopressor treatment. Notably, anti-hypertensive medication was ongoing at the time of

treatment with Pexa-Vec prior to the development of hypotension in the majority of these patients, thereby potentially exacerbating the potential for hypotension.

Risk mitigation strategies for hypotension with Pexa-Vec are addressed in section **3.2.1.1**.

3.4.1.3 Hematological Events

Transient decreases in WBC counts (including neutrophils and lymphocytes), platelets and hematocrit can occur. Transient thrombocytopenia (including reduced platelet count) occurred within days of treatment with Pexa-Vec and resolved within 1 week of treatment without medical intervention. Transient leukopenia (including reduced neutrophil and lymphocyte counts), has been observed with resolution generally occurring within 7 days of treatment. Leukopenia is a common finding associated with viral infection in general. Conversely, transient leukocytosis (including neutrophil, eosinophil, and monocyte subsets) has also been observed. An elevated WBC count is expected based on a GM CSF mediated effect by Pexa-Vec and the infusion of an attenuated vaccinia virus.

3.4.1.4 Chemistry Changes

Chemistry changes included hyponatremia and hyperglycemia; the relationship to Pexa-Vec treatment is not yet known. Dose-related direct hyperbilirubinemia (due to tumor swelling and occlusion of biliary tract drainage) has been noted in patients treated with Pexa-Vec whose liver tumors were adjacent to or impeding the biliary tract at baseline. In addition, acute respiratory distress secondary to airway obstruction was observed in one patient with HCC metastases to the lung following treatment. Therefore, patients with liver tumors in a location that would potentially result in significant clinical adverse effects if post-treatment tumor swelling were to occur, including at the site of the common bile duct, should not be included as per Exclusion Criteria. Biliary tract drainage should be considered as clinically indicated if biliary occlusion does not resolve quickly enough clinically. Acute post-treatment tumor swelling can result in hyperbilirubinemia within approximately one week following treatment; tumor swelling may resolve over time.

3.4.1.5 Rashes

Rashes related to latent virus reactivation have been reported, both with Varicella-Zoster (i.e., “shingles”) and herpes simplex virus; whether these rashes are related to Pexa-Vec itself, or due to the fever induced, is unknown. Small (<1 cm) superficial skin or oral mucous membrane pustules containing Pexa-Vec may develop after Pexa-Vec treatment. If they develop, it is typically within 1 week after the first IV infusion only. These pustules have rarely (<10%) been seen following IT injection. These pustules generally resolve within approximately the following 2–3 weeks, a time course that is consistent with the usual course following intentional vaccination with wild-type [non-attenuated] vaccinia vaccine. All pustules to date have been self-limited and resolved without complications or the need for specific anti-viral treatment.

3.4.1.6 Myocarditis

Wild type vaccinia has been associated with myocarditis. Around 1 in 175 patients administered with ACAM2000, a wildtype vaccinia (smallpox) vaccine, experienced myocarditis and/or pericarditis. To date, the use of Pexa-Vec (non-wild-type), in over 300 patients, has not been associated with myocarditis. The risk of myocarditis may be increased in the context of concomitant checkpoint inhibitors. For this reason, subjects with cardiovascular disease such as myocarditis and history of myocardial infarction are excluded from the study. Echocardiograms

will be performed at the screening and during the study if clinically necessary. Troponins will be monitored monthly during the study and follow up period.

3.4.1.7 Additional risks

Additional risks include tachycardia, portal vein thrombosis, cytokine release syndrome (CRS), viremia, herpes infections and hypertension

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the Pexa-Vec Investigator Brochure.

3.4.2 Potential Mechanisms of Pexa-Vec Shedding to the Environment, Biodissemination and Prevention of Transmission

3.4.2.1 Superficial Skin Pustules

Small (<1 cm) superficial skin or oral mucous membrane pustules containing Pexa-Vec may develop after Pexa-Vec treatment. If pustules develop, they do so typically within 1 week after the first administration. These pustules generally resolve within approximately the following 2–3 weeks, a time course that is consistent with the usual course following intentional vaccination with wild-type (non-attenuated) vaccinia vaccine. All pustules to date have been self-limited and resolved without complications or the need for specific anti-viral treatment.

The following steps should be carried out in the event of skin or oral mucosa pustule identification (patient or patient contact, which is unexpected):

- Record the AE (event term for Pexa-Vec related pustules must be recorded as "papularpustular rash").
- Instruct the patient/contact to cover the pustule with non-occlusive dressing (or wear a mask when around other people if oral lesions are present).

3.4.2.2 Urine, Feces, Blood, Throat and/or Saliva

Testing for the presence of Pexa-Vec after patient treatment has been conducted in several clinical studies in throat swabs, urine, feces, and blood samples. No person-to-person transmission of Pexa-Vec has been reported.

3.4.3 Adverse Events of Special Interest for Durvalumab and Tremelimumab

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

AESIs for durvalumab and tremelimumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-mediated adverse event (imAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate aetiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts

should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the Investigator has any questions in regard to an adverse event (AE) being an imAE, the Investigator should promptly contact MedImmune

AESIs observed with durvalumab and tremelimumab include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- Hepatitis / transaminase increases
- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis / serum lipase and amylase increases
- Myocarditis
- Myositis / Polymyositis
- Neuropathy / neuromuscular toxicity (i.e. Guillain-Barré, and myasthenia gravis)
- Intestinal Perforation

Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to:

- pericarditis,
- sarcoidosis,
- uveitis and other events involving the eye, skin,
- hematological and rheumatological events,
- vasculitis,
- non-infectious meningitis and non-infectious encephalitis

It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological aetiology are also considered AESIs.

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab and tremelimumab Investigator Brochure. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (please see **Appendix B**). These guidelines have been prepared by the Manufacturer to assist the Investigator in the exercise of his/her clinical judgment in treating these

types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

For durvalumab and tremelimumab, AESIs will comprise the following:

3.4.3.1 Pneumonitis: AEs of pneumonitis are also of interest, as pneumonitis has been observed with use of anti-PD-1 mAbs (but not with anti-PD-L1 mAbs). Initial work-up should include a high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended. Guidelines for the management of patients with immune-mediated AEs (imAEs) including pneumonitis are provided in **Appendix B**.

3.4.3.2 Infusion reactions: AEs of infusion reactions (also termed infusion-related reactions) are of special interest to AstraZeneca and are defined, for the purpose of this protocol, as all AEs occurring from the start of IP infusion up to 48 hours after the infusion start time. For all infusion reactions, SAEs should be reported to AstraZeneca Patient safety.

3.4.3.3 Hypersensitivity reactions: Hypersensitivity reactions as well as infusion-related reactions have been reported with anti PD-L1 and anti-PD-1 therapy [17]. As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of mAbs can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid reactions against the mAbs and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting, and unresponsiveness. Guidelines for the management of patients with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are provided in **Appendix B**.

3.4.3.4 Hepatic function abnormalities (hepatotoxicity): Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (e.g. cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the IP. Guidelines for management of patients with hepatic function abnormality are provided in **Appendix B**.

3.4.3.5 Gastrointestinal disorders: Diarrhea/colitis is the most commonly observed treatment emergent SAE when tremelimumab is used as monotherapy. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed. Guidelines on management of diarrhea and colitis in patients receiving tremelimumab are provided in **Appendix B**.

3.4.3.6 Endocrine disorders: Immune-mediated endocrinopathies include hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism. Guidelines for the management of patients with immune-mediated endocrine events are provided in **Appendix B**.

3.4.3.7 Pancreatic disorders: Immune-mediated pancreatitis includes autoimmune pancreatitis, and lipase and amylase elevation. Guidelines for the management of patients with immune-mediated pancreatic disorders are provided in **Appendix B**.

3.4.3.8 Neurotoxicity: Immune-mediated nervous system events include encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in **Appendix B**.

3.4.3.9 Nephritis: Consult with Nephrologist. Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc.)

Patients should be thoroughly evaluated to rule out any alternative etiology (e.g. disease progression, infections etc.)

Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade event. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in **Appendix B**.

3.5 Follow Up Period

Subjects will be followed up on a monthly basis until off-study criteria are met, with restaging scans being performed every 8 weeks.

3.6 Study Calendar

	Screening	Baseline	D -12	D -5	Cycle 1[i]					Cycle 2[i]					Cycle 3-4[i]				Cycle 5- Off Treatment [i]				FU [j]
					D 1	D 2	D 8	D 15	D 22	D 1	D 2	D 8	D 15	D 22	D 1	D 8	D 15	D 22	D 1	D 8	D 15	D 22	
Durvalumab [a]					X					X					X				X				
Tremelimumab [b]					X																		
Pexa-Vec [c]			X			X		X			X												
NIH Advance Directive Form [d]		X																					
Medical history	X																						
Concomitant meds		X			X					X					X				X				
Formal adverse event evaluation		X			X			X		X					X				X				X
Physical exam and ECOG	X	X [e]			X			X		X					X				X				X
Vital Signs	X	X [e]	X		X	X		X		X	X				X				X				X
CBC w/differential, Platelets [f]	X	X [e]		X	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
PT, INR, PTT, fibrinogen [f]		X			X					X					X				X				
Thyroid Panel [f]		X			X					X					X				X				

	Screening	Baseline	D -12	D -5	Cycle 1[i]					Cycle 2[i]					Cycle 3-4[i]				Cycle 5- Off Treatment [i]				FU [j]
					D 1	D 2	D 8	D 15	D 22	D 1	D 2	D 8	D 15	D 22	D 1	D 8	D 15	D 22	D 1	D 8	D 15	D 22	
Biochemical profile [f, n]	X	X [e]		X	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
24-hour urine per PI discretion	X																						
Urinalysis		X																					
ACTH, morning cortisol		X																					
Tumor marker CEA		X			X					X					X				X				
ECG	X	X [e]								X					X				X				
Echocardiogram [p]	X																						
Troponins		X			X					X					X				X				X
Restaging Radiologic Evaluation [g]	X	X [e]													X				X				
Tumor biopsy [h, m]		X			X					X					X [k]								
Immune monitoring [l]			X		X					X					X				X				
Blood for TCR beta sequencing [l]			X		X					X					X				X				

	Screening	Baseline	D -12	D - 5	Cycle 1[i]					Cycle 2[i]					Cycle 3-4[i]				Cycle 5- Off Treatment [i]				FU [j]
					D 1	D 2	D 8	D 15	D 22	D 1	D 2	D 8	D 15	D 22	D 1	D 8	D 15	D 22	D 1	D 8	D 15	D 22	
HIV, Hepatitis B and C serology and/or viral load	X																						
Serum or urine pregnancy test	X	X [e]																					
HLA		X																					
TB testing (if clinically indicated)	X																						
Histologic confirmation of dx	X																						
Microsatellite stability status	X																						
Cardiology consult as indicated [o]	X																						

[a] All patients will receive 1,500 mg of durvalumab via IV infusion on Day 1 of each cycle till patients meet off treatment criteria. A 1-hour observation period is required after the first infusion of durvalumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab infusion).

[b] Additionally, patients in Arms B1 and B2 will receive 300 mg of tremelimumab via IV infusion on Day 1 of cycle 1. Tremelimumab will be administered first. Durvalumab infusion will start approximately 1 hour after the end of tremelimumab infusion. The duration will be approximately 1 hour for each infusion. A 1-hour observation period is required after the first infusion of durvalumab and

tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab infusion).

[c]Pexa-Vec (JX-594) will be administered at a dose of 3 x 10^8 pfu (DL 1) or 1 x 10^9 pfu (DL 2) via IV infusion over 60 minutes (±5 minutes) for 4 doses only, beginning on Day – (minus) 12. Patients will be observed in the clinic and/or hospital for a minimum of 20 hours after the infusion. Treatments 2–4 may each be administered in a treatment window of ±3days.

[d]As indicated in section **12.3**, all subjects will be offered the opportunity to complete an NIH Advance Directive form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required.

[e] Tests done on screening do not need to be repeated on baseline if performed in designated time frame

[f] For all labs a '+/- 72hr' window applies, with the exception of those needed to determine proceeding with treatment. Labs may be performed outside of NIH.

[g] Restaging CT scan (or MRI if clinically indicated) every 8 weeks +/- 3 days to evaluate TTP in target lesion.

[h] Mandatory baseline and post-treatment tumor biopsies will be obtained on all patients, with the timing of second biopsy being determined by assignment on 1:1 basis.

[i] Cycles will be 28 days in length +/- 3 days.

[j] FU: Follow up visits once a month until patients are off study. If patients are not able to come to NIH, they will be followed by phone contact annually for survival, performance status, new cancer treatment.

[k] The biopsy around day 85 (Cycle 4 day 1) is optional

[l] Until PD while on protocol treatment, a '+/- 48hr' window applies

[m] Biopsy will have a window of +/-72 hrs. to allow for logistical issues; however, the biopsy will not be performed within 48 hrs. after Pexa-Vec administration

[n] Electrolytes, BUN, creatinine, AST, ALT, total and direct bilirubin, calcium, phosphorus, albumin, magnesium, uric acid, amylase.

[o] Performed in patients with history of cardiovascular disease. See section **2.1.2.10**

[p] Echocardiogram will be mandatory at the screening and performed during the study if clinically indicated.

3.7 Criteria for Removal from Protocol Therapy and Off Study Criteria

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 30, 60 and 90 days following the last dose of study therapy.

3.7.1 Criteria for removal from protocol therapy:

- Participant requests to be withdrawn from active therapy
- Unacceptable Toxicity as defined in section **3.1.1** and **Appendix B**
- Positive pregnancy test or intent to become pregnant
- Investigator discretion
- Initiation of alternative anticancer therapy including another investigational agent
- Progressive Disease. NOTE: While RECIST PD will be noted and recorded the immune-related RECIST criteria will be applied to determine discontinuation of study treatment.
- Subject who has received any amount of infliximab or other tumor necrosis factor alpha inhibitor
- Intercurrent illness that prevents further administration of treatment

3.7.2 Off Study Criteria

- Lost to follow-up

  Subjects will be considered lost to follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the subject's status at that time. Subjects who refuse continuing participation in the study including telephone contact should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing subjects throughout the study period. If contact with a missing subject is re-established, the subject should not be considered lost to follow-up and any evaluations should resume according to the protocol.

- Death
- Participant requests to be withdrawn from study
- Investigator discretion
- PI decision to end the study

4 CONCOMITANT MEDICATIONS/MEASURES

All routine and appropriate supportive care (including blood products) will be provided during this study, as clinically indicated, and in accordance with the standard of care practices. Clinical judgment should be utilized in the treatment of any AE experienced by the patient.

Information on all concomitant medications, administered blood products, as well as interventions occurring during the study must be recorded on the patient's eCRF in C3D.

4.1 Recommended Medications Related to Flu-like Symptoms related to Pexa-Vec

(mild-to-severe fever, rigors, anorexia, aches/pain, fatigue, headache, and/or nausea)

Acute Post-Treatment Symptom Management

During the post-treatment observation period, patients should receive IV solute-containing fluid and other measures (e.g. vasopressor therapy) per SOC as needed for blood pressure support. Anti-rigor medication (e.g. meperidine) or support medications may be used as needed.

Anti-emetics may be used at the Investigator's discretion for treatment of nausea or vomiting; it is noted, however, that corticosteroids should not be used.

Analgesics, anti-pyretics (e.g. prophylactic acetaminophen), antidepressants, bisphosphonates, EPO growth factors and other supportive care measures may be used at the Investigator's discretion.

4.2 Management of Hypotension and Contraindicated Treatments

To mitigate risk of hypotension following Pexa-Vec treatment, the following are required:

- Prehydration with 1 liter of solute-containing fluid (p.o. or IV) prior to each treatment
- Suspension of anti-hypertensive medication for 48 hours prior to and 48 hours after all Pexa-Vec treatments
- Anti-hypertensive medications include, but are not limited to, the following:
- Diuretics
- Beta-blockers
- ACE inhibitors
- Aldosterone agonists

4.3 Agents with Potential Inhibitory Activity Against Vaccinia Viruses

In the extremely unlikely case of generalized vaccinia virus infection, encephalitis or another clinically-significant, progressive toxicity that, in the opinion of the Investigator could be related to Pexa-Vec replication, Investigators may consider the use of agents with vaccinia inhibitory activity, if available in their country for such clinical use. Such agents may include anti-vaccinia immune globulin (VIG), cidofovir, and/or Arestvyr (USAN tecovirimat; ST-246). In addition, based on limited preclinical data, interferon, ribavirin, and sorafenib may have anti-vaccinia activity. For clarity, none of these agents have been used or approved for this purpose to date. Since these agents have not been used in Pexa-Vec treated patients to date, clinical judgment should be used when determining the optimal regimen and duration of treatment.

The availability of these or similar antiviral products is country-dependent; options will be investigated and a plan for a response to infection-related toxicities will be documented and communicated to study staff prior to initiation of the clinical trial.

4.4 Contraindicated Antiviral Therapy Shown to Inhibit Vaccinia Replication

- Cidofovir (except to treat toxicities potentially related to uncontrolled Pexa-Vec replication)

- Interferon/PEG-interferon, ribavirin

4.5 Contraindicated Treatments

- High dose systemic corticosteroids (defined as ≥20 mg/day prednisone or equivalent which is ongoing at the time of arm allocation and/or was taken for more than 4 weeks within the preceding 2 months of enrollment) or other immunosuppressive medications
- Anti-coagulation or anti-platelet medication that cannot be interrupted prior to study specified biopsies injections, including:
- Aspirin that cannot be discontinued for 7 days prior to biopsy
- Coumadin that cannot be discontinued for 7 days prior to biopsy
- LMWH that cannot be discontinued >24 hours prior to biopsy and UFH that cannot be discontinued >4 hours prior to biopsy (LMWH or UFH may be used to transition patients on and off the above anti-coagulants, if deemed appropriate by the treating physician) prior to Pexa-Vec treatments as long as the last dose of LMWH is administered 24 hours prior to biopsy and the last dose of UFH is administered >4 hours prior to treatments)
- Oral direct thrombin inhibitor (dabigatran) or direct Factor Xa inhibitor (rivaroxaban, apixaban, and edoxaban) that cannot be discontinued for 4 days prior to biopsy

4.6 Other Authorized Concomitant Treatments

- thrombopoietin, erythropoietin, G-CSF
- antidepressants
- steroids (NOTE: oral or parenteral steroids are not allowed during the Pexa-Vec treatment period, and for 1 week prior to and 2 weeks after Pexa-Vec treatment)
- topical therapies for symptomatic relief of hand-foot skin reaction and rash related to sorafenib
- bisphosphonates, vitamin B12 and vitamin D
- Hepatitis B antivirals are ALLOWED as DO NOT inhibit vaccinia virus replication: lamivudine, adefovir (and adefovir dipivoxil prodrug), telbivudine, tenofovir, emtricitabine, clevudine and entecavir. The ability of combinations of these agents to inhibit vaccinia virus replication has however not been evaluated. Therefore, combination therapy with anti-viral agents should be avoided if at all possible.

NOTES:

- Please contact MedImmune for any questions regarding management of immunosuppressive, anticoagulant, antihypertensive, or antiviral medications prior to treatments.
- Sites will be notified by MedImmune as additional information regarding allowed and contraindicated antivirals becomes available

4.7 Permitted concomitant medications for any combination of investigational drugs

Table 2. Supportive medications

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (e.g. acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc.])	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted
Hormone therapy for non-cancer diagnoses	Permitted

4.8 Excluded Concomitant Medications

Table 3. Prohibited concomitant medications

Prohibited medication/class of drug:	Usage:
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g. insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [e.g. by local surgery or radiotherapy])

Prohibited medication/class of drug:	**Usage:**
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding <<10 mg/day>> of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly. (Use of immunosuppressive medications for the management of IP-related AEs, premedication for patients who had infusion reaction, or in patients with contrast allergies is acceptable). In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.
Drugs with laxative properties and herbal or natural remedies for constipation	Should be used with caution through to 90 days after the dose of tremelimumab during the study
Sunitinib	Should not be given concomitantly or through 90 days after the dose of tremelimumab (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib)

4.9 Methods of contraception

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

4.9.1 Female patient of child-bearing potential

Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least 2 **highly** effective method of contraception (**Table 4.**) from the time of screening and must agree to continue using such precautions for 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy. Non-sterilized male partners of a female patient must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

4.9.2 Male patients with a female partner of childbearing potential

Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from screening through 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy. Eengaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.

Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (**Table 4.**).

N.B Females of childbearing potential are defined as those who are not surgically sterile (i.e. bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

4.9.3 Highly effective methods of contraception.

Highly effective methods of contraception, defined as one that results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly are described in **Table 4.** . Note that some contraception methods are not considered highly effective (e.g. male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 4. Highly Effective methods of contraception (<1% failure rate)

Barrier/Intrauterine methods	Hormonal Methods
• Copper T intrauterine device • Levonorgesterel-releasing intrauterine system (e.g. Mirena®)[a]	• Etonogestrel implants: e.g. Implanon or Norplant • Intravaginal device: e.g. ethinylestradiol and etonogestrel • Medroxyprogesterone injection: e.g. Depo-Provera • Normal and low dose combined oral contraceptive pill • Norelgestromin/ethinylestradiol transdermal system • Cerazette (desogestrel)

[a] This is also considered a hormonal method

4.10 Blood donation

Subjects should not donate blood while participating in this study, and for 3 months after the last durvalumab infusion or 6 months after the last dose of durvalumab + tremelimumab combination therapy, whichever comes later.

5 BIOSPECIMEN COLLECTION

5.1 Correlative Studies for Research

The correlative studies which we wish to perform are outlined below and summarized in the **Table 5.** A description of each test including a brief statement of rationale and processing information is made below.

Table 5. Biospecimen collection

Test/assay	Sample volume (approx)	Type of tube	Collection point	Location of specimen analysis[1]
Immune-monitoring	120mls (for PBMC)	EDTA	See Study Calendar **3.6**	Greten Lab
	5-10mls (for serum)	EDTA		
TCR beta sequencing	1ml (for PBMC)	EDTA	Study Calendar **3.6**	Adaptive Biotechnologies[2]
Immune cell infiltration, IHC, (CD3+ CD4/8 cells etc), PD-L1	tumor biopsy	NA	Study Calendar **3.6**	Greten Lab
TCR beta sequencing	tumor biopsy	NA	Study Calendar **3.6**	Adaptive Biotechnologies[2]
RNA Nanostring analysis (nCounterPan Cancer Immunology Profile)	tumor biopsy	NA	Study Calendar **3.6**	Greten Lab

[1] Blood samples will initially be sent to the Figg laboratory for barcoding and storage (See Section **5.2.1**).

[2] Lara Gruye, Adaptive Biotechnologies, 1551 Eastlake Ave E #200, Seattle, WA 98102 (855) 466-8667

5.1.1 Immune monitoring

We will analyze PBMC for quantitative and functional changes of effector cells as well as analyze sera for cytokines and chemokines. The effect on (i) CD4 T cell number and activity, (ii) CD8 T cell number and activity, (iii) NK cell number and activity, (iv) Treg number, (vi) MDSC: frequency + functional assay, (vii) selected cytokines in serum, and (viii) the detection of tumor-associated antigens using tetramer assay.

Patients will undergo blood sampling on the time points outlined in the Study Calendar **3.6**. Blood will initially be sent to the Figg laboratory for barcoding and processing.

On certain occasions the blood may also be brought to the Greten lab for processing and analysis.

5.1.2 Mandatory tumor biopsies

Tumor biopsies will be collected at baseline and either day 1 +/- 3 days or day 29+/- 3 days by the Interventional Radiology team by a percutaneous approach (note biopsy may not be collected within 48 hours after Pexa-Vec administration). It is preferred that at **least two core biopsies ≥18 gauge in diameter and ≥1 cm** in length will be obtained.
If a site is deemed appropriate for biopsy with minimal risk to the participant by agreement between the investigators and Interventional Radiology team, an attempt for biopsy will be made. The use of imaging to facilitate biopsies will be decided by members of the Interventional Radiology team and may include ultrasound, CT scan, PET scan or MRI. Should a CT scan be needed for biopsy, the number of scans for each procedure will be limited to the minimum number needed to safely obtain a biopsy. Tumor biopsies and local anesthesia will be administered only if they are considered to be of low risk to the participant, as determined by the investigators and Interventional Radiology. If an initial attempt at percutaneous biopsy is unsuccessful, the participant will be given an option to proceed with a repeated attempt at percutaneous biopsy.

5.1.3 Tumor tissue analysis

IHC will be performed on tumor tissue for assessment of immune cell infiltration (e.g. CD3+ CD4/8 cells etc.) as well as other surface markers such as PD-L1.

5.1.3.1 Optional Tumor Biopsy

A tumor biopsy may be performed at a subsequent timepoint (D85 approximately) if the patient is willing and the procedure can be performed safely. Tumor Tissue will be processed by the Department of Pathology, NCI, NIH (Dr. David Kleiner). Two core biopsies will be the attempted. Each specimen will be processed and analyzed as stated above.

5.2 Sample Storage, Tracking and Disposition

Samples will be ordered in CRIS Screens and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. All samples will be sent to Dr. Figg's lab for processing and storage until they are distributed to Dr. Greten's lab for sample analysis as described in the protocol.

Samples will not be sent outside the National Institutes for Health (NIH) without appropriate approvals and/or agreements, if required.

All samples will be barcoded, with data entered and stored in the secure databases. These databases create a unique barcode ID for every sample and sample box, which cannot be traced back to patients without database access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80^0C according to stability requirements.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in database. All researchers are required to sign a form stating that the samples are only to be used for research

purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

5.2.1 Samples Managed by Dr. Figg's Blood Processing Core (BPC)

5.2.1.1 BPC contact information

Please e-mail NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov .

5.2.2 Samples Managed by the Laboratory of Dr Greten

Contact information:

Sophie Wang

Building 10 Rm 3B44

Phone: 240-858-3218

E-mail: sophie.wang@nih.gov

5.2.3 Protocol Completion/Sample Destruction

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described in sections above. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed. If the patient withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reports will be made per the requirements of section **7.2**.

If the patient withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

5.3 Samples for Genetic/Genomic Analysis

5.3.1 TCR beta sequencing

TCR (cell receptor) gene usage may be quantitated in samples using conventional sequencing techniques of the T cell receptor variable region of the beta chain. Fewer than 100 genes will be analyzed. For TCR Beta Sequencing the NCI Thoracic and GI Malignancies Branch will release coded, linked tumor and PBMC samples to Adaptive Biotechnologies. Blood and tumor samples will be used.

5.3.2 Nanostring analysis (nCounterPan Cancer Immunology Profile)

Tumor samples will also be used for Nanostring analysis (nCounterPan Cancer Immunology Profile)

5.3.3 Privacy and Confidentiality of medical information/biological specimens

Fresh tumor and blood samples will be stored in a minus 80-degree freezer. Initially the samples of each patient will be sent to Dr. Figg's lab (**5.2.1**). At no time will patient's names be used on the blood and tissue samples. The molecular studies will be performed at the Adaptive Biotechnologies, 1551 Eastlake Ave E #200, Seattle, WA 98102 (855) 466-8667. Subject's genetic data will be deposited in a database such as dbGaP. Although there is controlled access to such a database, such a submission carries theoretical risks of revealing the identity of the subject. This is discussed in the consent.

5.3.4 Management of Results

The genetic testing performed on this protocol are not of sufficient scope to generate incidental findings and the results of molecular studies will not be communicated to the patient due to their investigational nature.

6 DATA COLLECTION AND EVALUATION

6.1 Data Collection

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (C3D) and Labmatrix ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the first study intervention, Study Day -12, through 90 days after the subject received the last study drug administration. Beyond 90 days after the last intervention, only adverse events which are serious and related to the study intervention need to be recorded.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

Adverse Events of grade 1 will not be collected.

End of study procedures: Data will be stored according to HHS, FDA regulations and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **7.2.1**.

6.2 Data Sharing Plans

6.2.1 Human Data Sharing plan

I will share coded, linked human data generated in this research for future research

- in a NIH-funded or approved public repository clinicaltrials.gov, dbGaP
- in BTRIS
- with approved outside collaborators under appropriate agreements
- in publication and/or public presentations

at the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 Response Criteria

For the purposes of this study, patients should be re-evaluated for response every 8 weeks (+/- 3 days). In addition to a baseline scan, confirmatory scans should also be obtained 4-8 weeks following initial documentation of objective response. Whilst immune-related RECIST criteria will be taken into consideration with regard to continuation of therapy in the event of growth (with a requirement for confirmation of PD), standard RECIST criteria will be the primary method used for evaluation of the primary endpoint.

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)[18]. 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.

6.3.1 Definitions

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

Evaluable for objective response

Only those patients who have measurable disease present at baseline, have received at least one dose of each agent, and have had their disease re-evaluated 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 each agent, 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.

6.3.2 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

- By chest x-ray: >20 mm;
- By CT scan:
  - Scan slice thickness 5 mm or under as >10 mm with CT scan
  - Scan slice thickness >5 mm: double the slice thickness
- With calipers on clinical exam: >10 mm.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm 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.

6.3.3 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 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 or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

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.

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.

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.

6.3.4 Response criteria

6.3.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

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

6.3.4.2 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 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).

6.3.4.3 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	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
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.
** Only for non-randomized trials with response as primary endpoint.
*** 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

6.3.5 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.

6.3.6 Modified Immune-related response criteria (irRC)

Modified immune-related response criteria (irRC) will also be employed in this study. This new classification is based on the recent learning from clinical studies with cancer immunotherapies that even if some new lesions appear at the beginning of a treatment or if the total tumor burden does not increase substantially, tumor regressions or stabilizations might still occur later. The irRC were created using bi-dimensional measurements (as previously widely used in the World Health Organization criteria). For this trial, the concepts of the irRC are combined with RECIST 1.1 to come up with the modified irRC. Please refer to **Appendix C** for further details.

6.3.7 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

6.4 Toxicity Criteria

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.3 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.3. A copy of the CTCAE version 4.3 can be downloaded from the CTEP web site (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_4.3). All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

7.1 Definitions

Please refer to definitions provided in Policy 801: Reporting Research Events found here.

7.2 OHSRP Office of Compliance and Training / IRB Reporting

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here. Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here.

7.3 NCI Clinical Director Reporting

Problems expeditiously reported to the OHSRP/IRB in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention **s**hould be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 INSTITUTIONAL BIOSAFETY COMMITTEE (IBC) REPORTING CRITERIA

7.4.1 Serious Adverse Event Reports to IBC

The Principal Investigator (or delegate) will notify IBC of any unexpected fatal or life-threatening experience associated with the use of Pexa-Vec oncolytic virus as soon as possible but in no event later than 7 calendar days of initial receipt of the information. Serious adverse events that are unexpected and associated with the use of Pexa-Vec oncolytic virus, but are not fatal or life-threatening, much be reported to the NIH IBC as soon as possible, but not later than 15 calendar days after the investigator's initial receipt of the information. Adverse events may be reported by using the FDA Form 3500a.

7.4.2 Annual Reports to IBC

Within 60 days after the one-year anniversary of the date on which the IBC approved the initial protocol, and after each subsequent anniversary until the trial is completed, the Principal Investigator (or delegate) shall submit the information described below. Alternatively, the NIH Intramural IRB continuing review report can be sent to the IBC in lieu of a separate report. Please include the IBC protocol number on the report.

7.4.3 Clinical Trial Information

A brief summary of the status of the trial in progress or completed during the previous year. The summary is required to include the following information:

- the title and purpose of the trial
- clinical site
- the Principal Investigator
- clinical protocol identifiers
- participant population (such as disease indication and general age group, e.g. adult or pediatric)
- the total number of participants planned for inclusion in the trial; the number entered into the trial to date whose participation in the trial was completed; and the number who dropped out of the trial with a brief description of the reasons
- the status of the trial, e.g. open to accrual of subjects, closed but data collection ongoing, or fully completed
- if the trial has been completed, a brief description of any study results.

7.4.4 Progress Report and Data Analysis

Information obtained during the previous year's clinical and non-clinical investigations, including:

- a narrative or tabular summary showing the most frequent and most serious adverse experiences by body system
- a summary of all serious adverse events submitted during the past year
- a summary of serious adverse events that were expected or considered to have causes not associated with the use of the gene transfer product such as disease progression or concurrent medications
- if any deaths have occurred, the number of participants who died during participation in the investigation and causes of death

  a brief description of any information obtained that is pertinent to an understanding of the gene transfer product's actions, including, for example, information about dose-response, information from controlled trials, and information about bioavailability.

7.5 NIH Required Data and Safety Monitoring Plan

7.5.1 Principal Investigator/Research Team

The clinical research team will meet on a weekly basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7.5.2 Safety Monitoring Committee (SMC)

This protocol will require oversight from the Safety Monitoring Committee (SMC). Initial review will occur as soon as possible after the annual NIH Intramural IRB continuing review date. Subsequently, each protocol will be reviewed as close to annually as the quarterly meeting schedule permits or more frequently as may be required by the SMC. For initial and subsequent reviews, protocols will not be reviewed if there is no accrual within the review period. Written outcome letters will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

8 SPONSOR PROTOCOL/SAFETY REPORTING

8.1 Definitions

8.1.1 Adverse Event

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

medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2))

8.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see section **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32)

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 4.3.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.1.6 Adverse Events of Special Interest (AESI)

See Section **3.4.3.**

8.2 Assessment of Safety Events

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis

and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to section **6.1**. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor with the exception of any listed in section **8.4**.

8.3 Reporting of Serious Adverse Events

Any AE that meets protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form.

All SAE reporting must include the elements described in section **8.2**.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=157942842

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 Waiver of expedited reporting to CCR

As death due to disease progression is part of the study objectives (OS) and captured as an endpoint in this study, death due to disease progression will not be reported in expedited manner to the Sponsor. However, if there is evidence suggesting a causal relationship between the study drug and the event, report the event in an expedited manner according to section **8.3.**

Hospitalization that is deemed to be due to disease progression, and not attributable to the intervention will not be reported as an SAE. The event, and the assessment that it was caused by disease progression will be documented in the medical records. The causality assessment of hospitalization will be re-evaluated any time when new information is received. If the causality assessment changes from disease progression to related to the study intervention, SAE report will be sent to the Sponsor in an expedited manner according to section **8.3**. If there is any uncertainty whether the intervention is a contributing factor to the event, the event should be reported as AE or SAE as appropriate.

8.5 Safety Reporting Criteria to the Pharmaceutical Collaborators

8.5.1 Reporting of serious adverse events

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of Pexa-Vec, durvalumab + tremelimumab or until the initiation of alternative anticancer therapy.

The investigator and/or sponsor must inform the FDA, via a MedWatch or equivalent, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32.

Such reports must be forwarded to AstraZeneca and Sillajen concurrently with submission to the FDA.

It is the responsibility of the sponsor to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca and Sillajen at the above timepoints.

A cover page should accompany the MedWatch or equivalent form indicating the following:

- "Notification from NCI Center for Cancer Research"
- NCI CCR IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number (ESR-16-11987) (AstraZeneca only)

Sponsor must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator.

Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox: AEMailboxClinicalTrialTCS@astrazeneca.com

Send SAE report and accompanying cover page by way of email to Sillajen's designated mailbox: safetyCRC027@sillajen.com

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca, Sillajen and the FDA.

8.5.2 Overdose

Any overdose of a study subject with durvalumab + tremelimumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the Sponsor and AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox : AEMailboxClinicalTrialTCS@astrazeneca.com. If the overdose results in an AE, the AE must also be recorded as an AE. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE. There is currently no specific treatment in the event of an overdose of durvalumab or tremelimumab.

The investigator will use clinical judgment to treat any overdose.

An overdose of a study subject with Pexa-Vec should be reported to the designated safety mailbox: safetyCRC027@sillajen.com. If the overdose results in an AE or SAE, these should be reported as such.

8.5.3 Hepatic function abnormality

Hepatic function abnormality (as defined in Section **3.4.3.4**) in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" within 24 hours of knowledge of the event to the sponsor and AstraZeneca/MedImmune Patient Safety using the designated Safety e-mailbox

AEMailboxClinicalTrialTCS@astrazeneca.com, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study subject will be based on the clinical judgment of the investigator.

If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor and AstraZeneca/MedImmune.

8.6 Reporting Pregnancy

8.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy become known,

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (see section **8.1.2)** should be reported as SAEs.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented.

8.6.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of durvalumab+ tremelimumab combined therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 180 days after the last dose of durvalumab+ tremelimumab combined therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period after the last dose should, if possible, be followed up and documented.

8.7 Regulatory Reporting for Studies Conducted Under CCR-Sponsored IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

9 CLINICAL MONITORING

As a sponsor for clinical trials, FDA regulations require the CCR to maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary and secondary study endpoints; adherence to the protocol, regulations, ICH E6, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment.

The monitoring program also extends to multi-site research when the CCR is the coordinating center.

This trial will be monitored by personnel employed by a CCR contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct

10 STATISTICAL CONSIDERATIONS

The primary objective of this study is to determine the response rate of Pexa-Vec oncolytic virus in combination with immune checkpoint inhibition in patients with refractory metastatic colorectal cancer based on investigator evaluation.

Based on our analysis of data from previous trials of patients with similar eligibility requirements the typical response rate is much less than 10%.

For Arm A2, provided that adequate safety has been demonstrated, a total of 10 evaluable patients will be enrolled and treated at DL2. The following table shows the probability of having 1 or more responses or 2 or more responses out of 10 patients as a function of the underlying true probability of a response:

True response	No. of responses	Probability

True response	No. of responses	Probability
0.02	1+	0.18
	2+	0.016
0.05	1+	0.40
	2+	0.086
0.15	1+	0.80
	2+	0.46
0.25	1+	0.94
	2+	0.76
0.30	1+	0.97
	2+	0.85

Thus, observing 2+ responses out of 10 evaluable patients would have 8.6% probability of occurring if the true probability of a response rate were 5% and would have 76-85% probability of occurring if the true probability of a response were 25-30%. As such, it would be desirable if 2 or more responses out of 10 could be noted to rule out 5% and demonstrate consistency with a 25% or greater response rate. However, in the context of this preliminary pilot trial, observing a single response in 10 patients would provide limited evidence of at least 15% true response probability and thus suggests that may be minimal evidence for benefit. As a further aid to interpretation, the exact two-tailed 80% confidence interval about 1/10 is 0.01 to 0.34, and the exact two-tailed 80% confidence interval about 2/10 is 0.05-0.45.

Biopsies from patients treated at DL2 will be taken pre-treatment and then half the patients will receive a second biopsy at day 1 and the other half at day 29. Thus, within Arm A2, 5 patients will be expected to have paired results from biopsies based on day 1- baseline and 5 will be expected to have paired results from biopsies based on day 29-baseline. Any statistical evaluations made for the 5 patients within each set of paired biopsy results will be considered exploratory, and the results will not be adjusted for multiple comparisons. With 5 patients in a paired comparison, there would be 90% power to identify a change from baseline equal to 2.0 SD of the difference (effect size 2.0), or 71% power to identify a change with effect size 1.5, using a 0.05 significance level paired t-test. In practice, Wilcoxon signed rank tests may be used unless the differences are shown to be consistent with a normal distribution ($p>0.05$ by a Shapiro-Wilks test).

After completion of Arm A2, a decision will be made – after review of all the clinical, safety and correlative data – whether to proceed with Arm B1 at that time. The same statistical considerations will apply to Arm B2 as in Arm A2. Formal comparison between the two arms will not be possible given patient numbers and will be considered hypothesis generating for future development.

To address safety, tolerability and feasibility of Pexa-Vec oncolytic virus in combination with immune checkpoint inhibition, adverse events will be tabulated by grade according to CTCAE and analyzed and reported descriptively.

In addition to evaluation of the proportion of patients that are progression-free at 5 months, the progression-free survival for patients will also be analyzed via a Kaplan-Meier curve. This curve will be compared informally to other published results in similar patients. As well, the overall response rate will be reported and the overall survival will be reported using a Kaplan-Meier curve.

It is anticipated that up to 12 patients per year will be able to enroll onto this protocol. It is expected that accrual of up to 26 total patients will be required to complete this protocol, but up to 32 may be needed if DL1 requires 6 patients at each dose level. Thus, accrual is expected to be completed in approximately 2 to 3 years. In order to allow for a small number of unevaluable patients, the accrual ceiling will be set at 35 patients.

11 COLLABORATIVE AGREEMENT

11.1 Cooperative Research and Development Agreement (CRADA)

11.1.1 Medimmune/Astrazeneca

The CRADA (02853) for this protocol is finally executed between Thoracic & GI Malignancies Branch, NCI, NIH and Medimmune/Astrazeneca, the manufacturer of Tremelimumab and Durvalumab

11.1.2 Sillajen Inc.

The CRADA (03163) for this protocol is finally executed between Thoracic & GI Malignancies Branch, NCI, NIH and Sillajen Inc. the manufacturer of Pexastimogene Devacirepvec (Pexa-Vec)

11.2 Material Transfer Agreement (MTA)

An MTA with Adaptive Biotechnologies (40860-16) is in place to perform the studies on coded, linked samples indicated in sections **5.1** and **5.1.3**.

12 HUMAN SUBJECTS PROTECTIONS

12.1 Rationale for Subject Selection

Subjects treated on this study, will be individuals with metastatic colorectal cancer, which has recurred (or persisted) after appropriate standard treatment. Individuals of any gender, race or ethnic group will be eligible for this study. Eligibility assessment will be based solely on the patient's medical status. Recruitment of patients onto this study will be through standard CCR mechanisms. No special recruitment efforts will be conducted.

12.2 Participation of Children

Individuals under the age of 18 will not be eligible to participate in this study because they are unlikely to have colorectal carcinoma, and because of unknown toxicities in pediatric patients.

12.3 Participation of subjects unable to give consent

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisional impaired. For this reason and because there is a prospect of direct benefit from research participation (section **12.5**), all subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate.

For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIH HRPP SOP 14E for appointing a surrogate decision maker for adult subjects who are (a) decisional impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

12.4 Evaluation of Benefits and Risks/Discomforts

Patients will receive evaluation of their disease at the National Cancer Institute's Clinical Center. This protocol may or may not benefit an individual, but the results may help the investigators learn more about the disease and develop new treatments for patients with this disease.

Potential adverse reactions attributable to the administration of Pexa-Vec and the chemotherapeutic agents utilized in this trial are discussed in section **3.4**. All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. Patients will be examined and evaluated prior to enrollment. All evaluations to monitor the treatment of patients will be recorded in the patient chart. If patients suffer any physical injury as a result of the participation in this study, immediate medical treatment is available at the Clinical Center, National Cancer Institute, Bethesda, Maryland.

Although no compensation is available, any injury will be evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations. In all publications and presentations resulting from this trial, patients' anonymity will be protected to the maximum extent possible. Authorized personnel from the National Cancer Institute (NCI) and Food and Drug Administration (FDA) or other regulatory authorities may have access to research files in order to verify that patients' rights have been safeguarded. In addition, patient names will be given to the Central Registration to register and verify patients' eligibility.

12.5 RISKS/BENEFITS ANALYSIS

12.5.1 Risk of Biopsy

All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks (such as bleeding, infection and visceral injury) that will be explained fully during informed consent.

12.5.2 Risks of exposure to ionizing radiation

The study will involve radiation from the following sources:

- Up to 7 CT scans per year for disease assessment
- Up to 3 CT scans for the collection of 2 mandatory and 1 optional biopsy

Subjects in this study may be exposed to approximately 10.1 rem per year. This amount is more than would be expected from everyday background radiation. Being exposed to excess radiation can increase the risk of cancer. The risk of getting cancer from the radiation exposure in this study is 1 out of 100 (1%) and of getting a fatal cancer is 0.5 out of 100 (0.5%).

12.5.3 Risks of CT Scans

In addition to the radiation risks discussed above, CT scans may include the risks of an allergic reaction to the contrast. Participants might experience hives, itching, headache, difficulty breathing, increased heartrate and swelling.

12.5.4 Research Blood Collection Risks

Risks of blood draws include pain and bruising in the area where the needle is placed, lightheadedness, and rarely, fainting. When large amounts of blood are collected, low red blood cell count (anemia) can develop.

12.5.5 Other Risks/Benefits

The potential benefit to a patient that goes onto study is a reduction in the bulk of their tumor which may or may not have favorable impact on symptoms and/or survival. Potential risks include the possible occurrence of any of a range of side effects which are listed in the Consent Document. The procedure for protecting against or minimizing risks will be to medically evaluate patients on a regular basis as described.

12.5.6 Risks/Benefits Analysis

It is possible that treatment on this protocol may reduce tumor burden or lessen symptoms caused by the cancer. While treatment on this protocol may not individually benefit subjects, the knowledge gained from this study may help others in the future who have colorectal cancer. Potential risks include the possible occurrence of any of a range of side effects listed above. The risks and benefits of participation for adults who become unable to consent, are no different than those described for patients who are less vulnerable.

12.6 Consent Process and Documentation

The informed consent document will be provided to the participant for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms) per discretion of the designated study investigator and with the agreement of the participant. Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

13 PHARMACEUTICAL INFORMATION

13.1 Tremelimumab (17363)

13.1.1 Source

Tremelimumab will be supplied by AstraZeneca/MedImmune, Inc.

13.1.2 Toxicity

See **Appendix B** for details.

13.1.3 Formulation and preparation

Tremelimumab is a human IgG2 anti-CTLA-4 mAb that is being developed as an immunotherapeutic agent for various cancers.

Investigational Product	**Manufacturer**	**Concentration and Formulation as Supplied**
Tremelimumab	AstraZeneca/ MedImmune	Tremelimumab will be supplied by AstraZeneca either as a 400-mg or a 25-mg vial solution for infusion after dilution. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 5.5 and density of 1.034 g/mL. The nominal fill volume is 20.0 mL for the 400-mg vial and 1.25 mL for the 25-mg vial. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original container until use to prevent prolonged light exposure.

The 20 mg/mL solution will be diluted into a 0.9% Sodium Chloride bag for IV infusion. Vials containing tremelimumab may be gently inverted for mixing but should not be shaken.

For dose preparation steps, the following ancillary items are required:

- IV infusion bags of 0.9% sodium chloride injection (250 mL size). 0.9% Sodium Chloride bags must be latex-free and can be made of polyvinyl chloride (PVC) or polyolefins (e.g., polyethylene), manufactured with bis (2-ethylhexyl) phthalate (DEHP) or DEHP-free.
- IV infusion lines made of PVC/DEHP or PVC/tri octyl trimellitate (TOTM) or polyethylene or polyurethane. All DEHP-containing or DEHP-free lines are acceptable. Lines should contain a 0.22 or 0.2 µm in-line filter. The in-line filter can be made of polyethersulfone (PES) or polyvinylidine fluoride DRF (PVDF). Lines containing cellulose-based filters should not be used with tremelimumab.
- Catheters/infusion sets made of polyurethane or fluoropolymer with silicone and stainless steel and/or PVC components.
- Syringes made of polypropylene and latex-free. Polycarbonate syringes should not be used with tremelimumab.
- Needles made of stainless steel.

13.1.4 Stability and Storage

Tremelimumab does not contain preservatives and any unused portion must be discarded. Preparation of tremelimumab and preparation of the IV bag are to be performed aseptically. Total in-use storage time for the prepared final IV bag should not exceed 24 hours at 2-8°C or 4 hours

at room temperature (25°C). However, it is recommended that the prepared final IV bag be stored in the dark at 2-8°C until needed. The refrigerated infusion solutions in the prepared final IV bag should be equilibrated at room temperature for about 2 hours prior to administration. If storage time exceeds these limits, a new dose must be prepared from new vials.

The investigational product manager or qualified personnel will be responsible for preparing the IV doses using the following steps:

1) Select the IXRS-assigned number of vials of investigational product required to prepare the subject's dose.

2) All investigational product vials should be equilibrated to room temperature for 30 minutes prior to dose preparation.

3) To prepare the IV bag, first, calculate the dose volume of investigational product required. Second, remove the volume of 0.9% sodium chloride IV solution equivalent to the calculated dose volume of investigational product from the IV bag. Lastly, add the calculated dose volume of investigational product to the IV bag. Gently mix the solution in the bag by inverting up and down. Avoid shaking the IV bag to prevent foaming.

Labels will be prepared in accordance with Good Manufacturing Practice (GMP).

13.1.5 Administration procedures

Tremelimumab is to be administered as an IV solution at a rate of 250 mL/h.

In the event that either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Tremelimumab does not contain preservatives, and any unused portion must be discarded.

No incompatibilities between tremelimumab and polyvinylchloride or polyolefin have been observed. However, polycarbonate syringes and administration set containing cellulose-based filters should not be used with tremelimumab

13.1.5.1 Monitoring of dose administration

See Section **3.2.4**.

13.2 Durvalumab (17363)

13.2.1 Source

Durvalumab will be supplied by AstraZeneca/MedImmune Inc.

13.2.2 Toxicity

See **Appendix B** for details.

13.2.3 Formulation and Preparation

Durvalumab is a human monoclonal antibody of the immunoglobulin G1 kappa (IgG1κ) subclass.

Investigational Product	**Manufacturer**	**Concentration and Formulation as Supplied**

Durvalumab	Medimmune/AstraZeneca	Durvalumab will be supplied as a 500 mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Durvalumab must be used within the individually assigned expiry date on the label.

13.2.4 Stability and Storage

The dose of durvalumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration.

Protect from light.

13.2.5 Administration procedures

No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed. Dose of 1500mg durvalumab for patients >30 kg will be administered using an IV bag containing 0.9% (w/v) NaCl or dextrose, with a final durvalumab concentration ranging from 1 to 20 mg/mL and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Remove 30.0 mL of IV solution from the IV bag prior to addition of durvalumab. Next, 30.0 mL of durvalumab (i.e., 1500 mg of durvalumab) is added to the IV bag such that final concentration is within 1 to 20 mg/mL (IV bag volumes 100 to 1000 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Durvalumab will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral or central vein. Following preparation of

durvalumab, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2, or 0.22-µm in-line filter.

The IV line will be flushed with a volume of IV solution (0.9% [w/v] NaCl equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed. In the event that either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab (MEDI4736) does not contain preservatives, and any unused portion must be discarded.

13.2.5.1 Monitoring of dose administration

See Section **3.2.4**

13.2.5.2 Dose Calculation

Note: The dosing for durvalumab will be a flat dosing of 1500mg.

The corresponding volume of investigational product should be rounded to the nearest tenth of a mL (0.1 mL). Each vial contains a small amount of overage and the overage should be utilized as much as possible before using another vial.

The number of vials required for dose preparation is the next greatest whole number of vials from the following formula: Number of vials = Dose (mL) ÷ 20 (mL/vial)

13.2.5.3 Investigational Product Preparation Steps (Durvalumab)

The investigational product manager or qualified personnel will be responsible for preparing the IV doses using the following steps:

1) Select the IXRS-assigned number of vials of investigational product required to prepare the subject's dose.
2) All investigational product vials should be equilibrated to room temperature for 30 minutes prior to dose preparation.
3) To prepare the IV bag, first, calculate the dose volume of investigational product required. Second, remove the volume of 0.9% sodium chloride IV solution equivalent to the calculated dose volume of investigational product from the IV bag.
4) Lastly, add the calculated dose volume of investigational product to the IV bag. Gently mix the solution in the bag by inverting up and down. Avoid shaking the IV bag to prevent foaming.
5) Labels will be prepared in accordance with Good Manufacturing Practice (GMP).

13.2.5.4 Investigational Product Inspection

Each vial selected for dose preparation should be inspected.

If there are any defects noted with the investigational product, the investigator and site monitor should be notified immediately. Refer to the Product Complaint section (**13.2.5.6**) for further instructions.

During the inspection if the solution is not clear or any turbidity, discoloration or particulates are observed, notify your site monitor and store the vial(s) in QUARANTINE at refrigerated (2-8ºC) temperature for drug accountability and potential future inspection.

Notify the IXRS that the unusable vials are damaged. The IXRS will indicate the replacement vials. Select appropriate replacement vials for the preparation of the subject's dose and perform the same inspection on the newly selected vials. For accountability, record the total number of vials removed from site inventory. Used vials should be held for accountability purposes at ambient storage temperature.

13.2.5.5 Investigational Product Accountability

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. All unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune.

13.2.5.6 Reporting Product Complaints

Any defects with the investigational product must be reported *immediately* to the MedImmune Product Complaint Department by the site with further notification to the site monitor. All defects will be communicated to MedImmune and investigated further with the Product Complaint Department. During the investigation of the product complaint, all investigational products must be stored at labeled conditions unless otherwise instructed.

Product defects may be related to component, product, or packaging and labeling issues. The list below includes, but is not limited to, descriptions of product complaints that should be reported.

Component Issue: Defect in container or dosing mechanism of the investigational product. The component defect may be damaged, missing, or broken. Component examples include vials, stoppers, caps, spray barrels, spray nozzles, or plungers.

Product Issue: Defect in the product itself. The product appearance has visual imperfections such as foreign particles, crystallization, discoloration, turbidity, insufficient volume, or anything that does not apply to the product description.

Packaging/Labeling Issue: Defect in the packaging or labeling of the product. The packaging or labeling defects may be damaged or unreadable, or the label may be missing.

When reporting a product complaint, site staff must be prepared to provide the following information:

1) Customer information: reporter name, address, contact number, and date of complaint

2) Product information: product name, packaging kit number or lot number, expiry date, and clinical protocol number

3) Complaint information: complaint issue category and description

MedImmune contact information for reporting product complaints:

Email: productcomplaints@medimmune.com

Phone: +1-301-398-2105 +1-877-MEDI-411 (+1-877-633-4411)

Fax: +1-301-398-8800

Mail: MedImmune, LLC Attn: Product Complaint Department One MedImmune Way, Gaithersburg, MD USA 20878

13.3 Pexa-Vec (17363)

13.3.1 Source

Pexa-Vec will be supplied by Sillajen Inc.

13.3.2 Toxicity

Toxicity of Pexa-Vec listed in Section **3.4.1**

13.3.3 Formulation and Preparation

VACC-6.25.1, Recombinant Vaccinia/GM-CSF (VAC-6.25.1 [GM-CSF1]),

VAC GM-CSF, Vaccinia/GM-CSF

Generic Name: Recombinant Vaccinia GM-CSF; RAC VAC GM-CSF (thymidine kinase-deactivated plus GM-CSF)

Pexa-Vec is a viral suspension supplied in individual 4-mL glass vials. Each vial contains Pexa-Vec diluted in 30 mM Tris 10% Sucrose buffer. The recoverable volume of Pexa-Vec in each vial is 2 mL with an infectious titer of 1×10^9 pfu (9.0 Log pfu). Each vial is intended for single use (i.e., 1 injection to 1 patient). 0.6 ml of viral suspension is to be removed for the 3×10^8 pfu dose

13.3.3.1 Packaging and Labeling of Pexa-Vec

Each vial is packed in a cardboard box (secondary packaging) which constitutes a Pexa-Vec treatment kit (1-vial treatment kit).

The primary labels on the vials as well as the secondary labels on the cardboard boxes are in the language of countries where the study is to be performed. Labels are compliant with local regulatory requirements and contain information including, but not limited to: Sponsor name, product code, lot number, concentration, volume, storage conditions, route of administration and a cautionary statement in proper language.

13.3.3.2 Biosafety/Containment Level Classification of Pexa-Vec

Pharmacies, hospitals, and clinics routinely administer infectious organisms (e.g., live viral vaccines, and live BCG for bladder cancer) and Pexa-Vec preparation and administration handling recommendations are also based on CDC guidelines for preparation of the standard vaccinia vaccine (CDC 2009). Pexa-Vec is classified as a biohazard safety level 1 or 2 (BSL-1 or 2) agent based on the very low pathogenicity and the potential to spread only by direct physical contact

13.3.3.3 Transport of Pexa-Vec

13.3.3.4 Interstate and International Transport

Pexa-Vec is shipped on dry-ice with the official transport designation as a “Biological Substance, Category B” in compliance with International Air Transportation Association and Department of Transportation regulations and other local regulations for air and road transport of infectious substances (UN 3373 regulations).

13.3.3.5 Transport within the Institution

All transport of Pexa-Vec (in vial or IV bag) within the institution must be done using a leak-proof container/bag clearly-marked with a biohazard symbol.

13.3.4 Stability and Storage

Pexa-Vec must be stored at or below –60°C in an alarmed, temperature-monitored, secure freezer with restricted access. Pexa-Vec can be stored with other therapeutics but should be separate from lab samples.

The study demonstrated that the diluted Pexa-Vec is stable for 24 hours at 2^0 to 8^0 and an additional 3 hours at room temperature.

13.3.4.1 Dispensing of Pexa-Vec

Pexa-Vec will be dispensed only with the written authorization of the Investigator or a sub-Investigator to staff that have been specifically designated and trained for this study.

13.3.5 Handling of Pexa-Vec

All applicable institutional policies for preparation, transport, and disposal of viral vectors should be consulted and followed. During all Pexa-Vec manipulations gloves, gown, surgical mask and goggles (or safety glasses with side shields) must be worn. Headgear and overshoes are not mandatory.

Regardless of the BSL classification, the following are recommended as conservative measures for Pexa-Vec preparation, decontamination and storage:

13.3.5.1 Individuals excluded from handling (preparation and administration):

- pregnant or breastfeeding women
- immunocompromised individuals (e.g., organ transplant recipient, HIV-positive individual, or receiving chronic immunosuppressive medication)
- individuals with ongoing severe inflammatory skin condition requiring medical treatment or history of severe eczema requiring medical treatment.

13.3.5.2 Limit access:

- place a biohazard sign in the preparation area
- limit access to the designated area (e.g., the hood used to prepare Pexa-Vec) during preparation

13.3.5.3 Equipment

The following are recommended as conservative measures for Pexa-Vec preparation, decontamination and storage:

- Prepare in a Class IIA Biological Safety Cabinet (e.g., a standard chemotherapy hood equipped with a properly maintained high-efficiency particulate air [HEPA] filter)
- Wear standard PPE - gloves, goggles, mask, and gown while preparing the agent (e.g., as with standard chemotherapy precautions)

13.3.6 Preparation and administration of Pexa-Vec

The Pexa-Vec dose of 3 x 10^8 pfu (DL 1) or 1 x 10^9 pfu (DL 2) will be administered via IV infusion over 60 minutes (±5 minutes). Patients will receive 1 L 0.9% NaCl prior to infusion. This dose of Pexa-Vec will be suspended in a 255 mL infusion bag, containing 250 mL sterile 0.9% sodium chloride [NaCl] and 5 mL molar sodium bicarbonate (8.4% NaHCO3). The total amount of NaCl and NaHCO3 will approximately be 2.25 and 0.42 g/infusion, respectively.

13.3.7 Cleaning / Disinfection and Disposal

Standard institutional policies should be followed for cleaning and decontamination while handling vaccinia virus-based products. Hospital-grade chemical disinfectants containing: bleach (with at least 0.6% of active chlorine), alcohols (≥60%), aldehydes, hydrogen peroxide (3%), iodophor (75 ppm), phenols or quaternary ammonium compounds are adequate for routine cleaning and disinfection of work areas after Pexa-Vec handling. The manufacturer's instructions should be followed to ensure adequate contact time and confirm the ability of the equipment to withstand the disinfectant used.

All contaminated material (e.g., syringes, catheters, needles, tubing, gloves, used or unused vials, containers, bandages, etc.) should be disposed of in a clearly-marked biomedical waste container and discarded according to regular institution procedure for infectious waste i.e., autoclaving, incineration, or treatment with sodium hypochlorite solution. Biomedical waste will not be left unattended in a public area; autoclaved medical waste must not be disposed of as regular trash.

Textiles and fabrics can be laundered in hot water (71°C) with detergent and hot air drying.

13.3.8 Spills or Environmental Contamination

In the event of a spill, people in the immediate area will be alerted and other institutional personnel will be notified as required by institutional policies. Vaccinia viruses, like most enveloped viruses, are sensitive to inactivation by standard physical and chemical methods of disinfection. A standard hospital-grade disinfectant should be used to clean non-critical patient care equipment or medical devices between each patient use (e.g., bedpans, commodes, blood pressure cuffs, oximeters, glucose meters.) Hospital-grade disinfectants include 3% hydrogen peroxide, ≥60% alcohol, hypochlorite (1000 ppm), 0.5% accelerated hydrogen peroxide, quaternary ammonium compounds, iodophors (75 ppm), phenolics, and aldehydes. The manufacturer's instructions should be followed to ensure adequate contact time and confirm the ability of the equipment to withstand the disinfectant used. Critical

and semi-critical devices should be cleaned and reprocessed according to institutional guidelines.

Spills and accidents that result in overt exposures to infectious material will be reported as required by institutional policies.

13.3.9 Unused Drug Return or Destruction

During the course of the study and at termination of the study all unused Pexa-Vec patient kits will be destroyed locally or returned to the drug supply provider.

For local destruction, the Investigator/Pharmacist or delegated person will ensure that all contaminated material should be disposed of in a clearly-marked biomedical waste container and discarded according to regular institution procedure for infectious waste and will not expose

humans to any risks from Pexa-Vec. A certificate of destruction will be completed. The drug supply provider will coordinate the return of all unused Pexa-Vec patient kits. A certificate of return will be completed and provided to the drug supply provider (copy retained by the site).

Upon completion or termination of the study at a site, the monitor will verify that all used Pexa-Vec patient kits have been decontaminated (if applicable) and disposed, all unused Pexa-Vec patient kits have been returned or destroyed, and no IP remains on site.

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15 APPENDICES

15.1 Appendix A-Performance Status Criteria

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

15.2 Appendix B – Tremelimumab and Durvalumab Dosing Modifications

Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy With Tremelimumab or Tremelimumab Monotherapy) 17 October 2019 Version (CTCAE v4.03)

General Considerations regarding Immune-Mediated Reactions

Dose Modifications

Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03 (unless indicated otherwise).

In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions:

- Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** of the start of the immune-mediated adverse event (imAE)
- Grade 3 recurrence of a previously experienced treatment-related imAE following resumption of dosing

Grade 1 No dose modification

Grade 2 Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1.

If toxicity worsens, then treat as Grade 3 or Grade 4.

Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper.

Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions:

1. The event stabilizes and is controlled.
2. The patient is clinically stable as per Investigator or treating physician's clinical judgement.
3. Doses of prednisone are at ≤10 mg/day or equivalent.

Toxicity Management

It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table:

- It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines.
- Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow.
- Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events.
- For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.
- Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation.
- If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper).
- More potent immunosuppressives such as TNF inhibitors (e.g., infliximab; also refer to the individual sections of the imAEs for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are

Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy With Tremelimumab or Tremelimumab Monotherapy) 17 October 2019 Version (CTCAE v4.03)

General Considerations regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
Grade 3 Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below. **Grade 4** Permanently discontinue study drug/study regimen. Note: For asymptomatic amylase or lipase levels of >2.0×ULN, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).	not currently noted in the guidelines – when these events are not responding to systemic steroids. – With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. – Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; imAE immune-mediated adverse event; IV intravenous; NCI National Cancer Institute; PO By mouth.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider Pulmonary and Infectious Disease consults.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or

			anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections)[a] − Consider Pulmonary and Infectious Disease consults. − Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** − Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. − Obtain Pulmonary and Infectious Disease consults; consider, as necessary, discussing with study physician. − Hospitalize the patient. − Supportive care (e.g., oxygen). − If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Diarrhea/Colitis **Large intestine perforation/Intestine perforation**	**Any Grade**	**General Guidance**	**For Any Grade:** − Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). − When symptoms or evaluation indicate a perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay. − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. − Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to

		prevent potential progression to higher grade event, including perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool) (Perforation: symptomatic; medical intervention indicated*) * "medical intervention" is not invasive	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks[a]. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

	Grade 3 or 4 (Grade 3 Diarrhea: stool frequency of ≥7 over baseline per day; Grade 4 Diarrhea: life threatening consequences) (Grade 3 Colitis: severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs; Grade 4 Colitis: life-threatening consequences, urgent intervention indicated) (Grade 3 Perforation: severe symptoms, elective* operative intervention indicated; Grade 4 Perforation: life-threatening consequences, urgent intervention indicated) *This guidance anticipates that Grade 3 operative interventions of perforations are usually not elective	**Grade 3** Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. **Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g., infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients**	**Any Elevations in AST, ALT or TB as Described Below**	**General Guidance**	**For Any Elevations Described:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	AST or ALT >ULN and ≤3.0×ULN if baseline normal, 1.5-3.0×baseline if baseline abnormal; and/or TB > ULN and ≤1.5×ULN if baseline normal, >1.0-1.5×baseline if baseline abnormal	• No dose modifications. • If it worsens, then treat as described for elevations in the row below.	– Continue LFT monitoring per protocol.
	AST or ALT >3.0×ULN and ≤5.0×ULN if baseline normal, >3-5×baseline if baseline abnormal; and/or TB >1.5×ULN and ≤3.0×ULN if baseline normal, >1.5-3.0×baseline if baseline abnormal	• Hold study drug/study regimen dose until resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal. • If toxicity worsens, then treat as described for elevation in the row below. • If toxicity improves to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal, resume study drug/study regimen after completion of steroid taper.	– Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal, in 1 to 2 days, consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work up and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

	AST or ALT >5.0×ULN if baseline normal, >5×baseline if baseline abnormal; and/or TB >3.0×ULN if baseline normal; >3.0×baseline if baseline abnormal	For elevations in transaminases ≤8×ULN and/or in TB ≤5×ULN if baseline normal, or for elevations in transaminases ≤8×baseline and/or TB ≤5×baseline if baseline abnormal: • Hold study drug/study regimen dose until resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal • Resume study drug/study regimen if elevations downgrade to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal, within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade as described in bullet above within 14 days For elevations in transaminases >8×ULN or elevations in TB >5×ULN if baseline normal, or for elevations in transaminases >8×baseline and/or TB >5×baseline if baseline abnormal, permanently discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.[b]	– Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Request Hepatology consult, and perform abdominal workup and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients** See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	**Any Elevations in AST, ALT or TB as Described Below**	**General Guidance**	**For Any Elevations Described:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg – For HCV+ patients: evaluate quantitative HCV viral load – Consider consulting hepatologist/Infectious Disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load >2000 IU/ml – Consider consulting hepatologist/Infectious Disease specialist regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥2-fold – For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above
	Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as described for elevations in the row below. For all transaminase elevations, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	

Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline **Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline**	• Hold study drug/study regimen dose untilresolution to AST or ALT ≤5.0×ULN. • If toxicity worsens, then treat as described for elevations in the rows below. If toxicity improves to AST or ALT ≤5.0×ULN, resume study drug/study regimen after completion of steroid taper.	– Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline **Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline**	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN • Resume study drug/study regimen if elevations downgrade to AST or ALT ≤5.0×ULN within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤5.0×ULN within 14 days Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider, as necessary, discussing with study physician. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

	Isolated AST or ALT >20×ULN, whether normal or elevated at baseline	Permanently discontinue study drug/study regimen.	**Same as above (except would recommend obtaining liver biopsy early)**
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR): - **Manage dosing for each level of transaminase rise as instructed for the next highest level of transaminase riseFor example, manage dosing for second level of transaminase rise (i.e., AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline, or AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline) as instructed for the third level of transaminase rise (i.e., AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline, or AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)** - **For the third and fourth levels of transaminase rises, permanently discontinue study drug/study regimen**			
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade**	**General Guidance**	**For Any Grade:** − Consult with nephrologist. − Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections). − Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.

Grade 1 (Serum creatinine > 1 to 1.5×baseline; > ULN to 1.5×ULN)	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
Grade 2 (serum creatinine >1.5 to 3.0×baseline; >1.5 to 3.0×ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
Grade 3 or 4 (Grade 3: serum creatinine >3.0×baseline; >3.0 to 6.0×ULN)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional

	(Grade 4: serum creatinine >6.0×ULN)		workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Rash or Dermatitis (including Pemphigoid)	**Any Grade** (refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED IF SUSPECT STEVENS-JOHNSON SYNDROME OR TOXIC EPIDERMAL NECROLYSIS.**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain Dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.

	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consult Dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). – For asymptomatic elevations in serum amylase and lipase >ULN and <3×ULN, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis,

		or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	**For Grade 2 (including those with symptomatic endocrinopathy):** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.

	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	**For Grade 3 or 4:** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). – Perform symptomatic treatment with Neurology consult as appropriate. –

	Grade 1	No dose modifications.	**For Grade 1:** – See "Any Grade" recommendations above.
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Obtain Neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g., IV IG).
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consider, as necessary, discussing with study physician. – Obtain Neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG). – Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade**	**General Guidance**	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly

		progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a Neurology consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a Neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 1	No dose modifications.	**For Grade 1:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a Neurology consult.
Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a Neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be

		administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** − Consider, as necessary, discussing with study physician. − Recommend hospitalization. − Monitor symptoms and obtain Neurology consult. *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. o If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective.

			○ Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
	Grade 1 (asymptomatic with laboratory [e.g., BNP] or cardiac imaging abnormalities)	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. - Consider using steroids if clinical suspicion is high.

	Grade 2, 3 or 4 (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support))	- If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Myositis/Polymyositis ("Poly/myositis")	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD.

		Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	Hold study drug/study regimen dose until resolution to Grade ≤1. - Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors

		(e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Grade 3 or 4 (pain associated with severe weakness; limiting self-care ADLs)	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** - Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

[a]ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.

[b]FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; imAE immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Infusion-Related Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade:** − Manage per institutional standard at the discretion of investigator. − Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1:** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2:** The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2:** − Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. − Consider premedication per institutional standard prior to subsequent doses. − Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** − Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

CTCAE Common Terminology Criteria for Adverse Events; IM intramuscular; IV intravenous; NCI National Cancer Institute.

Non–Immune-Mediated Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.

15.3 Appendix C: Modified immune-related response criteria (irRC)

This new classification is based on the recent learning from clinical studies with cancer immunotherapies that even if some new lesions appear at the beginning of a treatment or if the total tumor burden does not increase substantially, tumor regressions or stabilizations might still occur later. The irRC were created using bi-dimensional measurements (as previously widely used in the World Health Organization criteria). For this trial, the concepts of the irRC are combined with RECIST 1.1 to come up with the modified irRC.

For modified irRC, only target and measurable lesions are taken into account. In contrast to the RECIST 1.1 criteria, the modified irRC criteria (a) require confirmation of both progression and response by imaging at 6 weeks after initial imaging and (b) do not necessarily score the appearance of new lesions as progressive disease if the sum of lesion diameters of target lesions (minimum of 10 mm per lesion, maximum of 5 target lesions, maximum of 2 per organ) and measurable new lesions does not increase by ≥ 20%.

The same method of assessment and the same technique should be used to characterize each identified and reported target lesion(s) at baseline, during the trial, and at the end of trial visit. All measurements should be recorded in metric notation. The modified irRC based on RECIST 1.1 are displayed below.

Modified immune-related response criteria are defined as follows:

New measurable lesions: Incorporated into tumor burden.

New non-measurable lesions: Do not define progression but precludes (irCR).

Overall irCR:	Complete disappearance of all lesions (whether measurable or not) and no new lesions. All measurable lymph nodes also must have a reduction in short axis to 10 mm.
Overall irPR:	Sum of the longest diameters of target and new measurable lesions decreases ≥ 30%.
Overall irSD:	Sum of the longest diameters of target and new measurable lesions neither irCR, irPR, (compared to baseline) or irPD (compared to nadir).
Overall irPD:	Sum of the longest diameters of target and new measurable lesions increases ≥ 20% (compared to nadir), confirmed by a repeat, consecutive observations at least 4 weeks (normally it should be done at 6 weeks) from the date first documented.

Overall Responses Derived from Changes in Index, Non-Index, and New Lesions

Measurable Response	Non-Measurable Response		Overall Response Using Modified irRC
Index and New, Measurable Lesions (Tumor Burden)[1]	**Non-Index Lesions**	**New, Non-Measurable Lesions**	
Decrease 100%	Absent	Absent	irCR[2]
Decrease 100%	Stable	Any	irPR[2]
Decrease 100%	Unequivocal progression	Any	irPR[2]
Decrease ≥ 30%	Absent / Stable	Any	irPR[2]
Decrease ≥ 30%	Unequivocal progression	Any	irPR[2]
Decrease < 30% to increase < 20%	Absent / Stable	Any	irSD
Decrease < 30% to increase < 20%	Unequivocal progression	Any	irSD
Increase ≥ 20%	Any	Any	irPD

[1] Decreases assessed relative to baseline
[2] Assuming that the response (irCR and irPR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 weeks apart (normally it should be done 6 weeks apart).

15.4 Appendix D: List of Adverse Events related to study treatment before amendment D

	DL1 (N=3)			DL2 (N=12)											
Events	**#1**	**#2**	**#3**	**#4**	**#5**	**#6**	**#7**	**#8**	**#9**	**#10**	**#11**	**#12**	**#13**	**#14**	**#15**	**#16**
Fever	3		2	3	3	3	2	2	1	2	3	3	2	3	2	2
Hypotension	1			2	2	1	2	1	2	1		2	1		2	2
Chills	1	1	1	2		1	2			2	2	2		1	1	2
Fatigue	1		1				1	1	2				1	1	1	
Papulopustular Rash					1	1	1	1	1	1						
Sinus Tachycardia				1					2	1		1		1	1	1
Vomiting				1				1	1	1						
Nausea				1			1	1	1	1	1					
Flu Like Symptoms	1							1	2						1	
Headache				1				1	2							
Nasal Congestion															1	1
Pain	1								2							
Constipation								1								
Cough																1
Cramp					2											
Hypertension								2							1	
Elevated ALT	2							1		1		1				
Elevated AST	2							1		1		1				
Elevated ALP	2							1				1				
Elevated Bilirubin	1															

Lymphopenia	**1**					**1**	**4**						**1**	**2**	**3**	**2**
Neutropenia									**3**	**1**						
Anemia						**2**		**2**		**1**		**1**	**2**	**3**	**1**	
Hyperuricemia				**1**					**1**							
Decreased platelet count															**1**	
Hyponatremia				**1**	**1**			**1**				**1**				
Hypophosphatemia				**2**												
Hypomagnesemia									**1**							
Hypercalcemia															**1**	
Hypoalbuminemia						**2**	**1**									
Elevated Lipase	**1**			**1**												
Elevated Amylase											**1**					
Increased Creatinine					**2**											