To: CTEP Protocol and Information Office

From: Stephen Ansell, MD, PhD; J.C. Villasboas, MD

Date: February 18, 2021

Re: Protocol Amendment #8 (PVD 17Feb2021) in response to RRA from CTEP (28Jan2021) for NCI protocol #10089: "A Randomized Phase 2 Study of Varlilumab (CDX-1127) in Combination with Nivolumab in Patients with Relapsed or Refractory Aggressive B-cell Lymphomas"

SUMMARY OF CHANGES:
Protocol (PVD 02/17/2021)

I. Response to Request for Amendment from CTEP:

#	Section	Comments

1.	7.1.1.2	V2.3 of the CAEPR for nivolumab has been replaced with V2.4. Changes include:
		• The SPEER grades have been updated.
		• Added New Risk:
		  • Less Likely: CD4 lymphocytes decreased
		  • Rare: Enterocolitis; Eye disorders - Other (Vogt-Koyanagi-Harada); Hepatobiliary disorders - Other (immune-mediated hepatitis); Renal and urinary disorders - Other (immune-mediated nephritis)
		• Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
		  • Added: CD4 lymphocytes decreased
		• Provided Further Clarification:
		  • Immune system disorders - Other (sarcoid granuloma) is now reported as Immune system disorders - Other (sarcoidosis).

A Randomized Phase 2 Study of CDX-1127 (Varlilumab) in Combination with Nivolumab in Patients with Relapsed or Refractory Aggressive B-cell Lymphomas

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Participating Organizations:

LAO-11030 / University Health Network Princess Margaret Cancer Center LAO **Note: Participation is restricted to sites located in the United States**
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LAO-CT018 / Yale University Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / University of Pittsburgh Cancer Institute LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO
LAO-NCI / National Cancer Institute LAO
EDDOP / Early Drug Development Opportunity Program
CATCHUP / Creating Access to Targeted Cancer Therapy for Underserved Populations

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NCI-Supplied Agents:
CDX-1127 (Varlilumab) (NSC 778372)
Nivolumab (BMS-936558, MDX-1106, and ONO-4538) (NSC #748726)

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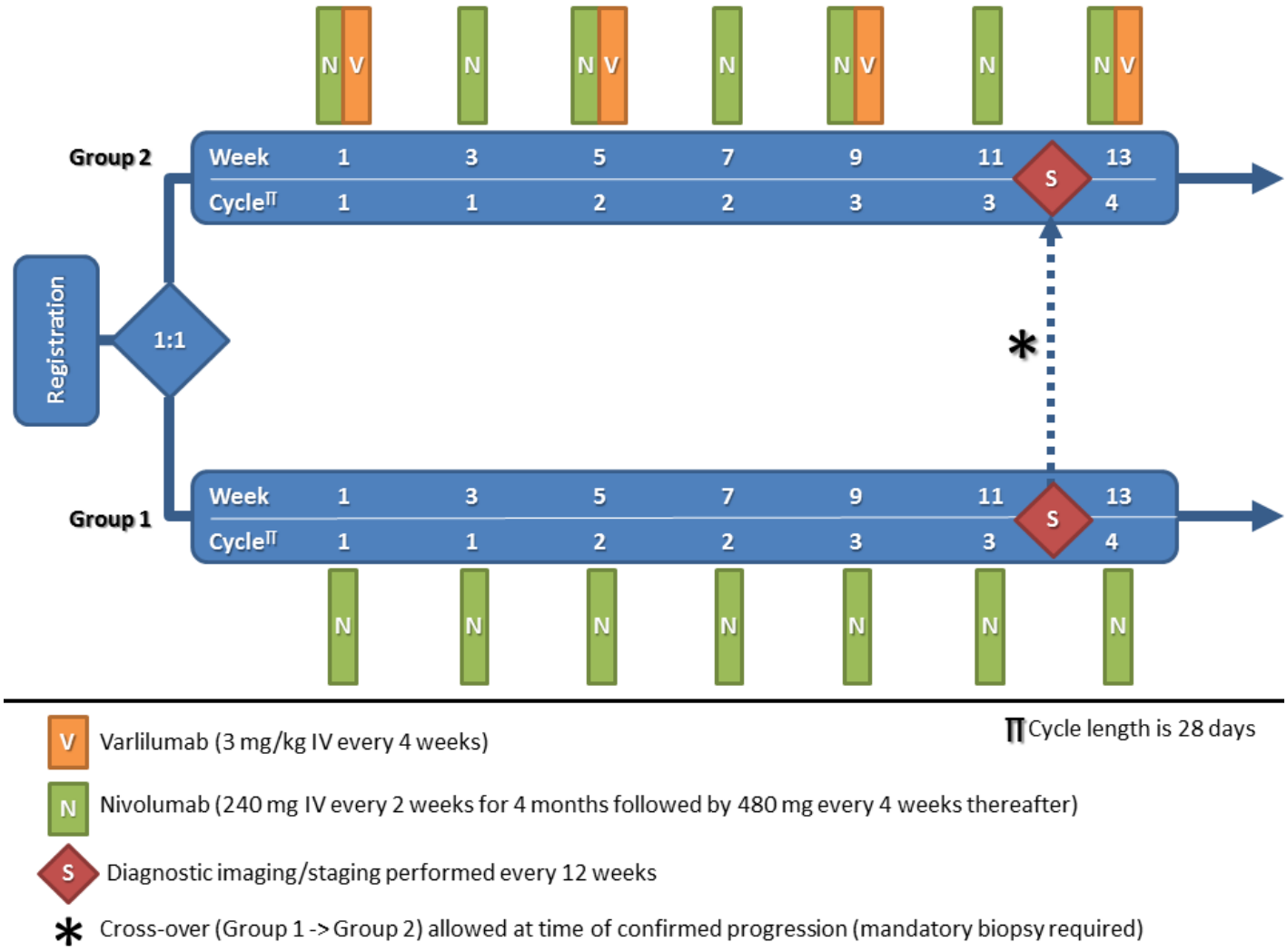
SCHEMA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V Varlilumab (3 mg/kg IV every 4 weeks)
∏ Cycle length is 28 days
N Nivolumab (240 mg IV every 2 weeks for 4 months followed by 480 mg every 4 weeks thereafter)
S Diagnostic imaging/staging performed every 12 weeks
* Cross-over (Group 1 -> Group 2) allowed at time of confirmed progression (mandatory biopsy required)

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1.1 Primary Objectives

1.1.1 To determine the anti-tumor activity of combination therapy with CDX-1127 (varlilumab) and nivolumab as compared to nivolumab alone in patients with advanced aggressive B-cell non-Hodgkin lymphomas (NHL) based on the lymphoma response to immunomodulatory therapy criteria or LYRIC (Cheson *et al*., 2016).

1.2 Secondary Objectives

1.2.1 To assess the safety and tolerability profile of treatment with a combination of CDX-1127 (varlilumab) and nivolumab in patients with advanced aggressive B-cell NHL.

1.2.2 To evaluate the duration of response, progression-free survival and overall survival

1.3 Exploratory Objectives

1.3.1 To determine the effect of combination therapy with CDX-1127 (varlilumab) and nivolumab on the immune system as assessed by immunohistochemistry (IHC), mass cytometry (CyTOF), changes in serum cytokine profile and immunogenicity assays.

1.3.2 To describe the pharmacokinetic profile of CDX-1127 (varlilumab) and nivolumab when used in combination.

2. BACKGROUND

2.1 Study Disease

Diffuse large B-cell lymphoma (DLBCL) remains the most common lymphoma worldwide and corresponded to 32.5% of a total of 596,476 non-Hodgkin lymphomas (NHL) diagnosed between 2008 and 2011 in the United States (Green *et al*., 2010 and Dong *et al*., 2002). Standard frontline treatment with chemo immunotherapy will cure about two thirds of these patients but a significant proportion will be either refractory to treatment or develop relapsed disease. Salvage treatment options in the relapsed/refractory settings are limited and most of these patients will unfortunately die from progressive disease.

Somatic alterations have been identified in DLBCL patients who fail to achieve durable remissions (Wilcox *et al*., 2009) but the role played by the host immune system in this context is unknown. Checkpoint blockade therapy is used in a variety of cancers and works by modulating the host's immune system towards an effective anti-tumoral attack. Trials using programmed cell death protein 1 (PD-1) inhibitors in advanced hematological malignancies demonstrated remarkable activity in patients with Hodgkin lymphoma (HL) (Yang *et al*., 2014, Yang *et al*., 2015), leading to the recent regulatory approval of Nivolumab in the United Stated. Unfortunately, results in the DLBCL cohort were marginal and short lived (Yang *et al*., 2012, Keir *et al*., 2008).

Therefore, there is a critical need to extend the benefits of immunotherapy to patients with advanced DLBCL and other aggressive NHL. We hypothesize that the combination of two immunomodulatory agents will increase the anti-tumor activity compared to single-agent Nivolumab and improve clinical outcomes for this group of patients with no significant increase in toxicity.

2.2 CTEP IND Agents

2.2.1 CDX-1127 (Varlilumab)

Antibodies that recognize immune cell surface molecules can be used to enhance or target immune responses against tumors. These include antibodies that activate antigen presenting cells (e.g. anti-CD40), antibodies that block immune checkpoints (e.g. anti-CTLA-4, anti-PD-1), and T cell costimulatory antibodies (e.g. anti-4-1BB). The costimulatory molecule CD27 is a member of the tumor necrosis factor (TNF) receptor superfamily, and is constitutively expressed on the majority of mature T-cells, memory B cells, and a portion of natural killer cells. The interaction of CD27 with its ligand CD70 plays key roles in the following processes:

- Co-stimulation through CD27 on T cells causes activation, proliferation, survival, and maturation of effector capacity and memory;
- Costimulation through CD27 on human B cells activates and promotes the generation of plasma cells, proliferation, and the production of immunoglobulin;
- Costimulation through CD27 on natural killer cells induces cytolytic activity.

Antibodies targeting CD27 can potentially be either agonists or antagonists of these CD27-CD70 pathway activities. In addition to the immune enhancing properties of agonist anti-CD27 mAbs, CD27-targeting antibodies may also provide direct therapeutic effects against tumors with CD27 expression. The expression of CD27 on various types of lymphomas and leukemias such as Chronic Lymphocytic Leukemia, Mantle Cell Lymphoma, Primary Central Nervous System Lymphoma, Burkitt's Lymphoma, and Marginal Zone B cell Lymphoma has been well documented (van Oers *et al.,* 1993; Ranheim *et al*., 1995; Trentin *et al*., 1997; Molica *et al.,* 1998; Murase *et al*., 1998; Dong *et al*., 2002). CD27 expression is present on most B cell malignancies at varying levels, and is also expressed by adult T-cell leukemia/lymphoma (van Oers *et al.,* 1993; Ranheim *et al.*, 1995; Shao *et al.*, 2010). CDX-1127 (Varlilumab) was selected on the basis of its agonistic properties and direct therapeutic effect against CD27 expressing tumors.

CDX-1127 (Varlilumab) is an agonist anti-CD27 monoclonal antibody that is expected to activate CD27 expressing T-cells in the context of T cell receptor stimulation. Based on strong pre-clinical efficacy data, other agonist antibodies recognizing lymphocyte costimulatory molecules, notably CD28, CD40, and CD137, have entered the clinic and have been associated with varying degrees of acute toxicity and clinical activity.

CD27 has distinct properties, including a restricted distribution of expression, requirement for concomitant T-cell receptor activation, comparable expression patterns in human and non-human primates in which toxicity studies have been conducted, and lack of observed toxicity in preclinical studies, that suggest agonist anti-CD27 monoclonal antibodies may have less acute toxicity than other agonist monoclonal antibodies targeting costimulatory molecules that have been studied in the clinic to date.

CDX-1127 (Varlilumab) binds to human CD27 and has shown strong reactivity with human lymphoma and leukemia cell lines, including the Burkitt's cell lines Raji, Daudi, and Ramos. CDX-1127 (Varlilumab) acts as an agonist of CD27 and reacts with the ligand binding site of CD27 as demonstrated by inhibition of CD70 binding to CD27. CDX-1127 (Varlilumab) does not bind other tumor necrosis factor receptor (TNFR) family members. As shown in both lymphocyte proliferation and cytokine induction studies, CDX-1127 (varlilumab) does not lead to direct activation of lymphocytes in the absence of signaling through the T cell receptor (TCR). BCL1 B-lymphoma and CT26 (colon cancer) tumor challenge models using human CD27-transgenic mice (Tg) showed treatment of mice with CDX-1127 (varlilumab) resulted in substantial improved survival at the higher dose levels (> 150 μg x 5) while a biologically effective response was observed for ≥ 0.5 mg/kg x 5 repeated dose in this model. CDX-1127 (Varlilumab) also showed significant anti-tumor effects against a variety of human tumor cell lines including Raji, Daudi, Namalwa and CCRF-CEM cell challenge in SCID mice.

T cell lymphomas and leukemias often express elevated levels of CD27, which could serve as a direct target for CDX-1127 (varlilumab). In fact, CDX-1127 (varlilumab) is effective against both T and B cell derived tumors in xenograft models. In addition, CDX-1127 (varlilumab) has potent anti-tumor activity against the EG7 mouse thymoma in syngeneic tumor models that rely on T cell mediated immunity for response. In vitro studies were conducted to investigate the effect of CDX-1127 (varlilumab) on proliferation and survival of CD27-expressing human T cell lines and primary T cell lymphomas or leukemia from patients. The CDX-1127 (varlilumab) antibody was coated to wells to provide optimal cross-linking of the CD27 receptor, and the results compared to an irrelevant human IgG1 isotype control. There was no evidence of enhanced tumor cell proliferation or viability in the presence of CDX-1127 (varlilumab). Some decrease in proliferation was observed by CDX-1127 (varlilumab), but additional studies will be required to determine if this effect is significant. Importantly, using CRF-CEM cells which are known to respond to anti-CD3, we did not observe increased viability with CDX-1127 (varlilumab), even in the context of T cell receptor stimulation. These studies demonstrate that crosslinking CD27 on human tumor cell lines or primary tumor cells of T cell origin does not significantly impact their growth or viability.

CDX-1127 (Varlilumab) has similar binding properties to human and non-human primate CD27. This has been demonstrated using recombinant purified protein from both species as well as by flow cytometry on relevant cell populations from peripheral blood and also by immunohistochemistry analysis on tissue sections. However, the pharmacological relevance of the monkey model to patients is not yet available.

In a preliminary non-GLP pilot toxicology study, single i.v. doses of CDX-1127 (varlilumab) administered to Cynomolgus macaques were well tolerated and no animals exhibited signs of toxicity over the 29 day follow-up. Clinical chemistry parameter values on Days 2, 3, and 8 were comparable to those observed at pre-dose with the exception of AST serum levels, which were increased in all animals at Day 2, possibly related to ketamine administration (Davy *et al.,* 1987, Gibhard *et al*., 2009). There were no major changes in circulating lymphocyte populations, with the exception of a transient decrease of natural killer cells.

In a repeat-dose GLP toxicology study in Cynomolgus macaques, five administrations of CDX-1127 (varlilumab), each one week apart, at the dose levels of 0, 0.25, 2.5 and 25 mg/kg/day did not result in any morbidity or mortality or changes in the assessed parameters of clinical condition, food appetence, body weights, body temperature, clinical pathology, ophthalmic and electrocardiography parameters, pathology (macroscopic, microscopic and organ weights) parameters and bone marrow smears. Anti-CDX-1127 (varlilumab) antibodies were detected in a very small proportion of 0.25 and 2.5 mg/kg/day treated animals at the end of dosing and detectable at the end of recovery in some animals. Peripheral blood mononuclear cell analysis at necropsy showed no significant changes in most cell populations. Altered regulatory T and natural killer cells in animals administered CDX-1127 (varlilumab) at 0.25 mg/kg/day were noted. Levels of IL-6 and IL-1β were undetectable in all animals at all timepoints. Approximately 58% of samples collected from animals in this study had detectable levels of IFN-γ. Samples with detectable levels were observed in animals from all dose levels (including controls) and at all timepoints. There was no correlation of the frequency of samples with detectable IFN-γ levels or mean IFN-γ levels with dose level or time after dosing. It was concluded that changes in IFN-γ levels were not test article related. There was evidence of systemic accumulation of CDX-1127 (varlilumab) at all dose levels, suggesting time-dependent kinetics; consistent with a slow elimination process as demonstrated by the low plasma clearance and long mean residence time and half-lives observed for CDX-1127 (varlilumab). Based on these results, the NOEL (no observable effect level) and NOAEL (no observable adverse effect level) of CDX-1127 (varlilumab) was considered to be 25 mg/kg/day administered once weekly to Cynomolgus monkeys for five weeks and two weeks of recovery.

A tissue cross-reactivity study was performed with observed tissue binding of CDX-1127 (varlilumab) being similar between human and Cynomolgus macaque tissues. Highly specific CDX-1127 (varlilumab)-FITC staining of mononuclear cells was observed and attributed to staining of target CD27 at the membrane and in the cytoplasm of these cells in human and Cynomolgus monkey tissues. Unexpected staining was observed in Cynomolgus monkey pituitary epithelium, but was restricted to the cytoplasm and did not correlate with any findings in the toxicology study. As a consequence of that, and the lack of such binding in human tissues, it is unlikely to be of clinical relevance.

A phase I study evaluated the safety, tolerability and efficacy of single-agent CDX-1127 (varlilumab) in patients with advanced hematologic malignancies (NCT01460134; Ansell et al, 2014). In the dose-escalation phase, patients received CDX-1127 (varlilumab) in 5

dose-levels ranging from 0.1 to 10 mg/kg IV weekly. A total of 24 patients with advanced hematological malignancies received single-agent CDX-1127 (varlilumab) given as a single dose followed by a 28-day observation period that was then followed by a multi-dose period consisting of 4 weekly doses followed by a 4-week observation period. Retreatment with up to 4 additional cycles (4 weekly doses followed by 8-week observation period) was allowed for patients with stable disease. No dose-limiting toxicity (DLT) was observed and MTD was not reached. Treatment-related adverse events were infrequent and nearly all mild to moderate in severity. No overlapping in toxicity with checkpoint inhibitor blockade therapy (endocrinopathies, colitis and pneumonitis) was observed. The half-life of CDX-1127 (varlilumab) ranged from 6 days (at 1 mg/kg) to 10.6 days (at 10 mg/kg) with linear pharmacokinetics. One patient experienced a complete response (a patient with heavily pretreated Hodgkin lymphoma treated at the 0.3 mg/kg dose-level) and 3 patients with NHL had stable disease with duration of response up to 14 months. Correlative studies demonstrated that treatment with CDX-1127 (varlilumab) was associated with reduction of circulating Treg and increase in pro-inflammatory cytokines.

2.2.2 Nivolumab

Nivolumab (BMS-936558, MDX-1106, and ONO-4538) is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) that is specific for human programmed death-1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor (Investigator Brochure, 2014). PD-1 is a negative regulatory molecule that is expressed transiently following T-cell activation and on chronically stimulated T cells characterized by an “exhausted” phenotype. Nivolumab binds to cynomolgus monkey PD-1 but not mouse, rat, or rabbit molecules. Clinical activity of nivolumab has been observed in patients with melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC). The combination of nivolumab and ipilimumab (anti-cytotoxic T lymphocyte associated antigen-4 [anti-CTLA-4]) in a phase 1/2 trial showed markedly enhanced clinical activity with an acceptable safety profile in melanoma patients (Wolchok *et al*., 2013).

The clinical use of monoclonal antibodies to T-cell inhibitory receptors has provided transformative information on the nature of the immune system and cancer. An emerging picture suggests that endogenous immune responses can mediate effective tumor regression and/or improved survival even in patients with large volume tumors resistant to other forms of therapy. Some of the unique features of this type of therapy, based largely on experience in advanced melanoma, include: improved overall survival (OS) with or without radiographic responses or improved progression-free survival (PFS); responses that may be delayed or occur after radiographic disease progression; combinations of immune modulators with enhanced or novel activities (in the example of ipilimumab and nivolumab); and toxicity that is almost exclusively immune or inflammatory in nature. It is not yet clear what factors determine responses and which components of the immune system are needed for this to occur. It seems likely that both memory helper and effector cells would be needed to sustain long-term responses. Increasing emphasis has been placed on understanding the relationships of the tumor,

cellular infiltrate, and immunologic milieu surrounding each tumor.

PD-1, a 55-kDa type 1 transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that include Ig super family member CD28, CTLA-4, inducible co-stimulator (ICOS), and B and T lymphocyte attenuator (BTLA) (Investigator Brochure, 2014). PD-1 is transiently but highly expressed on activated T cells functioning to limit immune effectors at the site of activation. Chronic stimulation may prevent the re-methylation of the PD-1 gene leading to continuous expression and characterizes a state of "exhausted" T cells that lose function and proliferative capacity while enhancing a suppressive tumor microenvironment. PD-1 may act together with other T-cell modulating molecules, including CTLA-4, TIM-3, lymphocyte-activation gene 3 (LAG-3) as well as indoleamine-pyrrole 2, 3-dioxygenase 1 (IDO-1), cytokines, and transforming growth factor beta (TGF-beta).

Two ligands specific for PD-1 have been identified: PD-ligand 1 (PD-L1, also known as B7-H1 or CD274, expressed on tumor, antigen-presenting cells [APCs], and dendritic cells [DCs]) and PD-L2 (also known as B7-DC or CD273, expressed on endothelial cells). The interaction of PD-1 with PD-L1 and PD-L2 results in negative regulatory stimuli that down-modulate the activated T-cell immune response through SHP-1 phosphatase.

PD-1 knockout mice develop strain-specific lupus-like glomerulonephritis (C57BL/6) and cardiomyopathy (BALB/c). In transplantable tumor models that expressed PD-1 and LAG-3 on tumor-infiltrating $CD4^+$ and $CD8^+$ T cells dual anti-LAG-3/anti-PD-1 antibody treatment cured most mice of established tumors that were largely resistant to single antibody treatment (Woo *et al*., 2012). Despite minimal immunopathologic sequelae in PD-1 and LAG-3 single knockout mice, dual knockout mice abrogated self-tolerance with resultant autoimmune infiltrates in multiple organs, leading to eventual lethality.

PD-L1 expression is found on a number of tumors, and is associated with poor prognoses based on OS in many tumors, including melanoma (Taube *et al*., 2012), renal (Thompson *et al*., 2004; Thompson *et al*., 2005; Thompson *et al*., 2006), esophageal (Ohigashi *et al.* 2005), gastric (Wu *et al*., 2006), ovarian (Dong *et al*., 2003), pancreatic (Nomi *et al*., 2007), lung (Zitvogel *et al*., 2006), and other cancers (Investigator Brochure, 2014).

The PD-1/PD-L1 axis plays a role in human infections, particularly in hepatitis C virus (HCV) and human immunodeficiency virus (HIV). In these cases, high expression levels of PD-1 were found in viral-specific $CD8^+$ T cells that also display a non-responsive or exhausted phenotype. Non-responsive PD-1-high T cells were observed in simian immunodeficiency virus (SIV) infection in rhesus macaques. Treatment of SIV-infected macaques with an anti-PD-1 mAb (3 mg/kg x4) resulted in decreased viral loads and increased survival along with expanded T cells with increased T-cell functionality.

2.2.2.1 Nonclinical Development of Nivolumab

In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab alone was well tolerated (Investigator Brochure, 2014). Combination studies have highlighted the potential for toxicity when combined with ipilimumab, MDX-1408, and BMS-986016. Nivolumab bound specifically to PD-1 (and not to related members of the CD28 family such as CD28, ICOS, CTLA-4, and BTLA) with a K_d = 3.06 nM. A surrogate rat anti-mouse PD-1 antibody (4H2) was derived and expressed as chimeric IgG1 murine antibody. Antitumor activity was seen for several tumor models, including colon carcinoma and fibrosarcoma.

2.2.2.2 Clinical Development of Nivolumab

Nivolumab is being evaluated as monotherapy and in combination with cytotoxic chemotherapy, other immunotherapy (such as ipilimumab), anti-angiogenesis therapy, and targeted therapies in completed and ongoing BMS-sponsored clinical trials in NSCLC, melanoma, RCC, hepatocellular carcinoma (HCC), gastrointestinal (GI) malignancies including microsatellite instability (MSI) in colorectal cancer, and triple-negative breast cancer (TNBC) with an expanding group of indications (Investigator Brochure, 2014). In addition, two investigator-sponsored trials (ISTs) of nivolumab in combination with a peptide vaccine in melanoma are being conducted in the adjuvant setting and advanced disease.

Seven nivolumab studies were conducted in Japan, including six studies in advanced solid tumors and recurrent or unresectable stage III/IV melanoma sponsored by Ono Pharmaceuticals Co. Ltd., and one IST in recurrent or advanced platinum-refractory ovarian cancer.

2.2.2.2.1. Pharmacokinetics

Pharmacokinetics (PK) of nivolumab was linear in the range of 0.3 to 10 mg/kg, with dose-proportional increases in maximum serum concentration (C_{max}) and area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), with low to moderate inter-subject variability observed at each dose level (Investigator Brochure, 2014). Clearance of nivolumab is independent of dose in the dose range (0.1 to 10 mg/kg) and tumor types studied. Body weight normalized dosing showed approximately constant trough concentrations over a wide range of body weights. The mean terminal elimination half-life of BMS-936558 is 17 to 25 days consistent with the half-life of endogenous IgG4.

2.2.2.2.2. Efficacy

In a phase 1 (1, 3, and 10 mg/kg nivolumab doses) dose-escalation study the 3 mg/kg dose was chosen for expanded cohorts. Among 236 patients, objective responses

(ORs) (complete or partial responses [CR or PR]) were seen in NSCLC, melanoma, and RCC. ORs were observed at all doses (Sznol *et al*., 2013). Median OS was 16.8 months across doses and 20.3 months at the 3 mg/kg dose. Median OS across all dose cohorts was 9.2 months and 9.6 months for squamous and non-squamous NSCLC, respectively (Brahmer *et al*., 2013). In the RCC cohort, median duration of response was 12.9 months for both doses with 5 of the 10 responses lasting ≥ 1 year (Drake *et al*., 2013).

In an advanced melanoma phase 1 study, nivolumab and ipilimumab were administered IV every 3 weeks for 4 doses followed by nivolumab alone every 3 weeks for 4 doses (concurrent regimen) (Wolchok *et al*., 2013). The combined treatment was subsequently administered every 12 weeks for up to 8 doses. In a sequenced regimen, patients previously treated with ipilimumab received nivolumab every 2 weeks for up to 48 doses. In the concurrent regimen (53 patients), 53% of patients had an OR at doses 1 mg/kg nivolumab and 3 mg/kg ipilimumab, with tumor reduction of 80% or more (modified World Health Organization [mWHO] criteria). In the sequenced-regimen (33 patients), the objective response rate (ORR) was 20%.

In a phase 1 study of nivolumab plus platinum-based doublet chemotherapy (PT-doublet) in chemotherapy-naïve NSCLC patients, 43 patients were treated with nivolumab + PT-doublet (Rizvi *et al*., 2013). No dose-limiting toxicities (DLTs) were reported and total/confirmed ORRs were 43/33%, 40/33%, and 31/31% in nivolumab/gemcitabine/cisplatin, nivolumab/pemetrexed/cisplatin, and nivolumab/carboplatin/paclitaxel arms, respectively.

2.2.2.2.3. Toxicology

A maximum tolerated dose (MTD) of nivolumab was not defined (Topalian *et al*., 2012). Serious adverse events (SAEs) occurred in 32 of 296 patients (11%) similar to the immune-related inflammatory events seen with ipilimumab: pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis (with noted pulmonary toxicity resulting in 3 deaths. Renal failure, symptomatic pancreatic and DM, neurologic events, and vasculitis have also been reported.). In combination with ipilimumab in the concurrent-regimen group (Wolchok *et al*., 2013), grade 3 or 4 treatment-related events were noted in 53% of patients. Skin rash represents the majority of these events.

2.2.2.2.4. Pharmacodynamics/Biomarkers

Tumor-cell expression (melanoma) of PD-L1 was characterized in combination with ipilimumab with the use of IHC staining and pharmacodynamics changes in the peripheral-blood absolute lymphocyte count (Wolchok *et al*., 2013). With PD-L1 positivity defined as expression in at least 5% of tumor cells, biopsy specimens from 21 of 56 patients (38%) were PD-L1–positive. Among patients treated with the

concurrent regimen of nivolumab and ipilimumab, ORs were observed in patients with either PD-L1–positive tumor samples (6 of 13 patients) or PD-L1–negative tumor samples (9 of 22). In the sequenced regimen cohorts, a higher number of overall responses was seen among patients with PD-L1–positive tumor samples (4 of 8 patients) than among patients with PD-L1–negative tumor samples (1 of 13) suggesting the possibility that these tumors have higher response rates to the combination. The relationship between PDL-1 expression and responses may not be present in patients treated with the combination. Tissue expression of PDL-2, interferon-γ (IFN- γ), IDO, and T cell $CD8^+$ are of current interest. Until more reliable data based on standardized procedures for tissue collection and assays are available, PD-L1 status cannot be used to select patients for treatment at this time.

2.3 Rationale

2.3.1 Combination Therapy using CDX-1127 (Varlilumab) and Nivolumab in Hematological Malignancies

Malignant cells are able to escape immune surveillance by co-opting cellular mechanisms such as immune checkpoint pathways (Green *et al*., 2010; Dong *et al*., 2002; Wilcox *et al*., 2009) or inducing T-cell exhaustion (Yang *et al*, 2014; Yang *et al*., 2015; Yang *et al*., 2012). These immune checkpoints are natural control mechanisms that prevent T-cell hyperactivation following an antigenic challenge (Keir *et al*., 2008; Francisco *et al*., 2010). The programmed death 1 (PD-1) pathway is an immune checkpoint with a clearly established role in tumor-mediated immunosuppression. Some neoplastic cells are able to express cognate ligands (PD-L1 and PD-L2) that are recognized by the PD-1 receptor expressed on the surface of activated effector T-cells. Activation of the PD-1: PD-L1/2 axis leads to a cascade of intracellular events that result in decreased T-cell survival and function. Monoclonal antibodies that recognize the PD-1 receptor are able to block its interaction with the ligands and result in release of an effective anti-tumoral immune response. Nivolumab is a fully human immunoglobulin G4 (IgG4) with high affinity against the PD-1 receptor with anti-tumoral activity against a number of solid tumors and hematological malignancies (OPDIVO Package Insert, 2014).

The single-agent safety and efficacy of nivolumab in hematological malignancies has been evaluated in a phase I dose-escalation study (NCT01592370). Patients with advanced hematological malignancies received nivolumab at a dose of 1 mg/kg with escalation to 3 mg/kg. Since the maximum tolerated dose (MTD) was not reached, patients in the expansion cohorts received 3 mg/kg at week 1, week 4, and then every 2 weeks. Results from the expansion cohort that included 23 patients with advanced classic Hodgkin lymphoma (CHL) have now been published (Ansell *et al*., 2014). Nivolumab was safe and well tolerated in this patient population and yielded an objective response in 20 patients (ORR 87%). Results from the experience in a small cohort of non-Hodgkin lymphoma (NHL) and other hematological malignancies demonstrated limited single agent activity in B-cell NHL (ORR 26%) multiple myeloma (ORR 4%), and T-cell NHL (ORR 17%) (Lesokhin *et al*., 2016).

T-cell exhaustion has been recognized as another important mechanism by which lymphoma cells escape an immune attack. Our group has demonstrated that the tumor microenvironment in NHL produces profound immunosuppression mediated by regulatory T-cells (T_{reg}) (Yang *et al*., 2006a; Yang *et al*., 2006b; Yang *et al*. 2007; Yang *et al*., 2009; Ai *et al*., 2009; Hilchey *et al*., 2007) and suppressive monocytic cells (SMC) (Wilcox *et al*., 2009; Xiu *et al.*, 2015). Strategies aimed at reversing T-cell exhaustion using agonistic molecules have the potential to produce an effective anti-tumoral response. The co-stimulatory molecule CD27 is constitutively expressed in many normal immune cells including T-cells, B-cells and NK cells van de Ven *et al*., 2015). T-cell function and survival is enhanced once CD27 binds to its ligand (CD70) on the surface of antigen presenting cells in the context of T-cell receptor engagement. Pre-clinical studies demonstrated that immune tolerance and exhaustion might be prevented or reversed by signaling through CD27. CDX-1127 (Varlilumab) is an agonistic IgG1 monoclonal antibody that recognizes CD27 (He *et al*., 2013; Vitale *et al*., 2012; Thomas *et al*., 2014). CDX-1127 (Varlilumab) has also demonstrated direct anti-tumoral activity in xenograft models of human lymphoma and leukemia cell lines via antibody-dependent cell-mediated cytotoxicity (ADCC). Given that CD27 expression has been demonstrated in many hematological malignancies (Dong *et al*., 2002), this constitutes another potential mechanism by which CDX-1127 (varlilumab) may enhance tumor eradication.

A phase 1 study evaluated the safety, tolerability and efficacy of single-agent CDX-1127 (varlilumab) in patients with advanced hematologic malignancies (NCT01460134) (Ansell *et al*., 2014). In the dose-escalation phase, patients received CDX-1127 (varlilumab) in 5 dose-levels ranging from 0.1 to 10 mg/kg IV weekly. A total of 24 patients with advanced hematological malignancies received single-agent CDX-1127 (varlilumab) given as a single dose followed by a 28-day observation period that was then followed by a multi-dose period consisting of 4 weekly doses followed by a 4-week observation period. Retreatment with up to 4 additional cycles (4 weekly doses followed by 8-week observation period) was allowed for patients with stable disease. No dose-limiting toxicity (DLT) was observed and MTD was not reached. Treatment-related adverse events were infrequent and nearly all mild to moderate in severity. No overlapping in toxicity with checkpoint inhibitor blockade therapy (endocrinopathies, colitis, and pneumonitis) was observed. The half-life of CDX-1127 (varlilumab) ranged from 6 days (at 1 mg/kg) to 10.6 days (at 10 mg/kg) with linear pharmacokinetics. One patient experienced a complete response (patient with heavily pretreated Hodgkin lymphoma treated at the 0.3 mg/kg dose-level) and 3 patients with NHL had stable disease with duration of response up to 14 months. Correlative studies demonstrated that treatment with CDX-1127 (varlilumab) was associated with reduction of circulating T_{reg} and increase in pro-inflammatory cytokines.

The preliminary results of a phase 1 dose-escalation study combining CDX-1127 (varlilumab) and nivolumab in advanced solid malignancies were recently released (Sanborn *et al*., 2016). A total of 35 patients with advanced solid tumors (colorectal cancer, melanoma, gynecological cancers and head/neck cancers) were treated with escalating doses of CDX-1127 (varlilumab) (0.1, 1.0 & 10 mg/kg) in combination with nivolumab (3 mg/kg) every 2 weeks for 4 doses. Repeat treatments with combination therapy were permitted for 4 additional cycles in patients deriving clinical benefit (stable

disease or better). Therapy was well tolerated and MTD was not reached. Correlative studies demonstrated increase in inflammatory cytokines, decrease in circulating CD4+ and regulatory T-cells as well as increase in tumor-infiltrating lymphocytes.

We hypothesize that combination therapy using a PD-1 inhibitor (nivolumab) and a CD27 agonist (CDX-1127; varlilumab) in patients with advanced hematological malignancies is safe and produces a synergistic effect compared to single-agent nivolumab. To test this hypothesis we propose a randomized phase 2 trial comparing single-agent immunotherapy using nivolumab versus dual immunotherapy (CDX-1127 (varlilumab) and nivolumab) in patients with relapsed or refractory aggressive B-cell NHL. Primary endpoint is response rate and patients in the control arm (nivolumab alone) would be allowed to cross over to the combination arm at the time of progression.

2.4 Correlative Studies Background

2.4.1 Integrated Biomarkers

2.4.1.1 Quantification and Characterization of CD27+ Cells in the Tumor Microenvironment by Immunohistochemistry (IHC)

The costimulatory molecule CD27 is a member of the tumor necrosis factor (TNF) receptor superfamily, and is constitutively expressed on the majority of mature T-cells, memory B cells, and a portion of natural killer cells. The interaction of CD27 with its ligand (CD70) plays key roles in activation, proliferation and survival processes of different immune cells. CD27 expression is also present on most B-cell malignancies at varying levels. It is therefore postulated that CDX-1127 (varlilumab) - an agonist anti-CD27 monoclonal antibody – may exert its anti-tumor activity through activation of CD27-expressing T-cells in the context of T cell receptor stimulation and also through direct cytotoxic activity on tumor cells expressing CD27.

We therefore hypothesize that the expression of CD27 in the tumor cells and/or on its surrounding microenvironment is required for CDX-1127's (varlilumab's) anti-tumoral activity. We further hypothesize that the level of expression of CD27 along with its localization (tumor cells vs. immune cells) may serve as a predictive biomarker for the activity of CDX-1127 (varlilumab) in patients with B-cell lymphomas. To test this hypothesis we will assess CD27 expression level and localization by IHC on tumor biopsies obtained at the time of registration from patients treated under this protocol. CD27 expression will not be required for participation in the study (integral biomarker). The level of CD27 expression along with its localization (tumor cells vs. immune cells) will be compared between patients who achieve clinical benefit from treatment with CDX-1127 (varlilumab). For patients in group 1 (nivolumab single-agent) who agree to undergo a repeat biopsy to confirm progression of disease and then cross over to group 2 (combinatory therapy with CDX-1127 (varlilumab) and nivolumab), the CD27 IHC assay will be repeated

and compared to baseline.

The CD27 expression evaluation via IHC will be performed centrally by Mosaic Laboratories, L.L.C. (12 Spectrum Pointe Drive, Lake Forest, CA 92630) using a proprietary assay using the rabbit mAb clone EPR8569 from Abcam. CD27 staining will be evaluated by image analysis using an Aperio image analysis algorithm and the final score will be expressed as % of cells at 0 (unstained), 1+, 2+ and 3+, in addition to number of CD27+ cells/mm2. Validation report can be provided upon request.

2.4.2 Exploratory Biomarkers

2.4.2.1 Comprehensive Analysis of Immune Cell Subpopulations using Mass Cytometry (CyTOF)

CyTOF (cytometry at time-of-flight) or mass cytometry is a new single-cell proteomics platform that uses mass spectrometry to evaluate more than 45 simultaneous parameters on a single-cell level (Bendall *et al*., 2012). This technology uses nonradioactive non-biological isotopes as reporters tagged to antibodies. Measurements are based on mass spectrometry, which largely avoids the hurdles of interference and spectral overlap seen with standard fluorescence-based flow cytometry. CyTOF is an ideal platform for the study of the tumor microenvironment given its ability to assess a large number of simultaneous parameters and resolve small differences in a heterogeneous population of cells. Taking advantage of the simultaneous assessment of several parameters per cell, CyTOF retains the ability to quantitate main lineage subsets in samples as small as 100,000 cells (Yao *et al*., 2015). This is particularly useful in situations where cell count is limited - such as tumor biopsies - or in the assessment of rare immune cell subsets.

CyTOF is therefore a powerful tool to study a complex biological system such as the microenvironment of B-cell lymphomas, especially in the context of a study using immune modulating drugs. Since both Nivolumab and CDX-1127 (varlilumab) may have a broad range of effects on different populations of cells – including tumor cells and host immune cells – an assay that simultaneously characterize these effects is necessary. The CyTOF assays will be performed on two different specimen types: (1) single-cell suspensions created from tumor samples obtained at the time of registration and at the time of treatment cross over (for patients in group 1) and on (2) peripheral blood mononuclear cells (PBMC) obtained before the infusion of the study drugs during the first 24 weeks of treatment.

Unstimulated specimens will be stained using a custom-designed 34-parameter global phenotyping panel recognizing 36 surface proteins and acquired on CyTOF2™. EQ™ Four Element Calibration Beads (Fluidigm) will be used for instrument calibration and normalization between experiments. Cisplatin (195Pt) will be used as a cell viability marker. The primary assay will allow identification of major immune cell populations (T-cells, B-cell, NK cell, monocyte/macrophages) along with detailed characterization of T-cell subsets (cytotoxic, regulatory, helper 1, helper 2,

helper 9, helper 17, helper 22, follicular helper, central memory, effector memory, naïve) and separately evaluate them for expression of markers of T-cell exhaustion (PD-1, LAG-3, TIM-3) and expression of co-stimulatory molecules (CD27, CD28, ICOS). Specimens with a surplus of cells will also be stained in parallel with a separate 22-parameter phenotyping panel recognizing surface and intracellular proteins in order to detail the phenotype of monocyte/macrophage subpopulations. See section 9.3 for details on the CyTOF assay panels. Analysis of immune cell subsets will be largely exploratory and reported descriptively.

2.4.2.2 Identification and Characterization of Intratumoral Immune Cells by Immunohistochemistry (IHC)

Expression of PD-L1 has been demonstrated to associate with clinical response of cancer patients treated with nivolumab. It is also postulated that CD8+ cytotoxic T-cell infiltration is critical to mediate anti-tumoral immunity in the context of PD-1 blockade. In the phase 1 trial dose-escalation study combining nivolumab with CDX-1127 (varlilumab) there was an increase in tumor-infiltrating lymphocytes (TILs) at all CDX-1127 (varlilumab) dose-levels. A trend towards increase in PD-L1 expression and CD8+ TILs was observed in patients with stable disease or better responses. Therefore, multiple markers including T cell, tumor cells, as well as related co-stimulatory and inhibitory markers will be stained to identify if there is any association of expression of these markers with the clinical activity of the study drugs.

Serial 4-µm paraffin-embedded sections will be used for IHC. The tissue will be deparaffinized with three changes of xylene and cleared through graded series of ethanol. Endogenous peroxidase will be quenched by incubation in 50% methanol/H2O2 and after rinsing with tap water; all sections will be pretreated for 30 minutes with 50 mmol/L EDTA using a steamer and cooled for additional 5 minutes. All staining will be done automatically on DAKO Autostainer using the following antibodies to CD11c (Leica Microsystems 5D11), CD14 (Cell Marque EPR 3653), CD163 (DAKO 1F8), CD68 (DAKO PG-M1), CXCL13 (R&D Systems 53610), FOXP3 (Abcam 236AE/7), CD3 (R&D Systems), PD-L1 (405.9A11), PD-L2 (366C.9E5), CD8a (Dako M7103) and PD-1 (Abcam NAT). The sections will be viewed with an Olympus BXFA51 microscope and pictures taken with an Olympus DP71 camera. Stained slides will be scored by expert hematopathologist. Analysis of intra-tumoral immune cell subsets by IHC will be largely exploratory and reported descriptively.

2.4.2.3 Evaluation of Genetic Alterations Involving Chromosome 9p24.1

PD-L1 overexpression on tumor cells can due to genetic lesions affecting the PD-L1 gene locus on chromosome 9 often through gene amplification or copy number variation. To evaluate if these genetic events are associated with response to therapy using nivolumab and CDX-1127 (varlilumab), we will perform fluorescent in-situ

hybridization (FISH) to assess copy number at chromosome locus 9p24.1. The bacterial artificial chromosome probes (CHORI; www.chori.org) RP11-599H2O, which maps to 9p24.1 and includes CD274 (encoding PD-L1, labeled with Spectrum Orange), and RP11-635N21, which also maps to 9p24.1 and includes PDCD1LG2 (encoding PD-L2, labeled with Spectrum Green), will be cohybridized. A control centromeric probe, Spectrum Aqua–labeled CEP9 (Abbott Molecular) that maps to 9p11-q11, will be hybridized according to the manufacturer's recommendations. Nuclei with a target: control probe ratio of at least 3:1 will be classified as amplified, those with a probe ratio of more than 1:1 but less than 3:1 will be classified as relative copy gain, and those with a probe ratio of 1:1 but with more than two copies of each probe will be classified as polysomic for chromosome 9p. Analysis of genetic alterations Involving chromosome 9p24.1 by FISH will be largely exploratory and reported descriptively.

2.4.2.4 Evaluation of Serum Cytokine Profile

Immunomodulatory drugs such as nivolumab and CDX-1127 (varlilumab) lead to changes in the tumor mileau through their interaction with different components of the immune system. Correlative studies from the early phase trials of single-agent CDX-1127 (varlilumab) and combinatory therapy using nivolumab and CDX-1127 (varlilumab) demonstrated increase in pro-inflammatory cytokines such as IL-12, MIP-1β, monocyte chemotactic protein 1 (MCP-1), monokine induced by interferon γ (MIG/CXCL9), inducible protein-10 (IP-10/CXCL10) and IL-6. The profile of cytokine elevation may therefore be associated with response to therapy with the study drugs and will be evaluated using a multiplexed assay.

Serial serum samples will be collected every 14 days before infusion of study drugs for the first 12 weeks of the study. Samples will be subjected to multiplex ELISA (Invitrogen, Camarillo, CA) to measure 30 serum cytokines. Luminex-200 system version 1.7 will be used for reading plates and MasterPlex QT1.0 system (MiraiBio) will be used to analyze data. Cytokines will include epidermal growth factor (EGF), eotaxin, basic fibroblast growth factor (FGF-b), granulocyte macrophage colony stimulating factor (GM-CSF), hepatocyte growth factor (HGF), IFN-α, IFN-ϒ, interleukin 1 receptor antagonist (IL-1RA), IL-1β,IL-2, IL-2R , IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17, IP10, MCP-1, MIG, MIP-1α (CCL3), MIP1β (CCL4), regulated on activation normal T-cell expressed and secreted (RANTES), TNF-α and vascular endothelial growth factor (VEGF). Internal control serum will be included in all assays to control for inter-assay variation. Analysis of the serum cytokine by multiplex ELISA will be largely exploratory and reported descriptively.

2.4.2.5 Evaluation of Mutational Burden as a Biomarker for Response to Checkpoint Blockade Therapy

As tumors accumulate mutations, they may become more prone to the generation of

neoantigens that can be recognized and targeted by the immune system. Solid tumor groups with a higher mutational burden – such as melanoma or mismatch repair deficient colorectal cancer – have demonstrated higher response rates to checkpoint blockade therapy as compared to tumors with fewer genetic lesions. Our study will therefore evaluate the mutational burden present in the tumor prior to initiation of therapy with the study drugs and describe their association with clinical outcomes.

Genomic DNA will be extracted from formalin-fixed, paraffin-embedded (FFPE) tissue blocks. Hematoxylin and eosin (H&E) stained sections from each case will be reviewed by an expert hematopathologist and representative blocks with at least 30% tumor cells will be selected. Sections of 10 x 4-micron dimensions will be cut from blocks (based on tissue area of 25 mm^2). DNA will be extracted using the Qiagen FFPE DNA extraction kit. DNA quantitation will be performed using a Qubit fluorometer prior to sequencing. Whole exome analysis of paired tumor and normal tissue will be performed using Ion TorrentTM platform at the Molecular Characterization and Clinical Assay Development Laboratory, Leidos Biomedical Research Inc., Frederick National Laboratory for Cancer Research. The analysis of mutational burden by whole exome sequencing is largely exploratory and reported descriptively.

2.5 Rationale for Modification of the Dosage of Nivolumab After 4 Months

Data obtained from manufacturer (Bristol-Myers Squibb) indicates that nivolumab administered as 480 mg Q4W over 30-minutes is expected to offer the same clinical benefit as 3 mg/kg Q2W in subjects with melanoma, squamous non-small cell lung cancer (SQ NSCLC), non-squamous NSCLC (NSQ, NSCLC), renal cell carcinoma (RCC), squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma (UC), and classical Hodgkin's lymphoma (cHL). This information is based upon data gathered in the course of the extensive nivolumab development program across multiple tumor types as well as robust clinical pharmacology and quantitative systems pharmacology (QSP) analyses.

The proposed dose modification is based on the comprehensive understanding of nivolumab pharmacology and mechanism of action taken together with the following data and analyses:

- Comparison of nivolumab exposures achieved by 240 mg Q2W, 480 mg Q4W and 3 mg/kg Q2W in subjects with melanoma, NSCLC, RCC, SCCHN, cHL, and UC

- Efficacy bridging evaluation
    - Comparison of the efficacy of nivolumab 3 mg/kg Q2W, 240 mg Q2W, and 480 mg Q4W in melanoma, NSCLC, and RCC with respect to the following endpoints: overall survival(OS), objective response (OR)
    - Comparison of predicted receptor occupancy (RO) with nivolumab 3 mg/kg Q2W, 240 mg Q2W, and 480 mg Q4W, including sensitivity of RO to parameters that may vary across solid tumor types

- Safety bridging evaluation
  - Assessment of safety margins, by comparison of predicted exposures with 240 mg Q2W and 480 mg Q4W relative to the well-tolerated 10 mg/kg Q2W regimen
  - Comparison of the safety of nivolumab 3 mg/kg Q2W, 240 mg Q2W, and 480 mg Q4W in subjects with melanoma, SQ and NSQ NSCLC, RCC, SCCHN, cHL, and UC with respect to the following 3 endpoints: Adverse events leading to discontinuation or death (AEDC/D), Grade 3+ adverse events (AE-Grade 3+), and Grade 2+ immune-mediated adverse events (AE-IM Grade 2+)
  - Clinical safety data from subjects treated with nivolumab 480 mg Q4W administered over a 30-minute infusion

The exposure-response efficacy analysis between the 3 mg/kg Q2W and the 480 mg Q4W regimens demonstrated that the hazard ratios for survival with the 480 mg Q4W regimen are very similar to the 3 mg/kg Q2W regimen, resulting in a similar hazard ratio relative to the standard of care treatment studied in each respective phase 3 clinical trial. In addition, these analyses indicated that similar outcomes would be achieved when using an early efficacy measure of response rate (objective response; OR) as well. The exposure-efficacy response trends were consistent across different tumor types with varying tumor immunogenicity and mutational burdens. Hence, in cases where nivolumab 3 mg/kg Q2W has been proven to be superior to standard of care, nivolumab 480 mg Q4W is predicted to provide comparable benefit, irrespective of tumor type.

This position is further supported by results of the analysis using a mechanistic quantitative systems pharmacology model incorporating transport to site of action, binding kinetics and varied physiological factors representing highly perfused or stromal tumors. The median intratumoral RO predicted with this model is high for nivolumab 3 mg/kg Q2W, 240 mg Q2W and 480 mg Q4W trough levels over a range of possible physiological parameter values. It is postulated that high RO at the tumor site will initiate the immuno-stimulatory cascade resulting in similar efficacy with 3 mg/kg Q2W, 240 mgQ2W, and 480 mg Q4W regimens.

Safety bridging was conducted using robust clinical data for the 10 mg/kg Q2W regimen that had a similar safety profile to the 3 mg/kg Q2W regimen. The nivolumab exposure parameters, including Cmax, resulting from 480 mg Q4W were well below Cmaxss values achieved with 10 mg/kg, providing a robust exposure safety margin. In addition, there were negligible differences in the probabilities of experiencing an adverse event irrespective of severity or adverse event type. Moreover, key safety results from the interim safety analysis of CA209511 (Part 2) demonstrate that the safety profile of nivolumab 480 mg IV over 30 minutes Q4W is consistent with the established safety profile of nivolumab (240 mg Q2W or 3 mg/kg Q2W administered IV over 60 minutes) across multiple indications and Summary of Product Characteristics [SmPC]. Taken together, these findings indicated that the safety profile of nivolumab is expected to be unaltered by the proposed dosing regimen changes.

Based on extensive quantitative clinical pharmacology analyses and safety analyses summarized in this submission, the nivolumab 480 mg Q4W regimen administered over 30 minutes is predicted to have similar efficacy and safety profiles to those established with the 3 mg/kg Q2W dosing regimen administered over 60 minutes. Thus, the provided analyses support the proposed nivolumab dosing regimen of 480 mg Q4W administered over 30 minutes as a convenient treatment option.

Based on this information the dosage of Nivolumab will be 240 mg IV every 2 weeks for the first 4 months on the study. After four months, Nivolumab will be administered at the dose of 480 mg IV every 4 weeks. Both dosage strengths will be infused over 30 minutes.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have a histopathologically confirmed diagnosis of an aggressive B-cell non-Hodgkin lymphoma that is recurrent or refractory to standard therapy.

For the purpose of this study, aggressive B-cell NHL will be deemed any lymphoma belonging to one of the following groups according to the 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms (Swerdlow *et al*., 2016).

For the purposes of stratification, diagnoses are grouped into 2 categories:

Category A
- Burkitt lymphoma
- Burkitt-like lymphoma with 11q aberration
- High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements
- High-grade B-cell lymphoma, NOS

Category B
- Diffuse large B-cell lymphoma (DLBCL), NOS
- Diffuse large B-cell lymphoma (DLBCL), NOS; Germinal center B-cell type
- Diffuse large B-cell lymphoma (DLBCL), NOS; Activated B-cell type
- Large B-cell lymphoma with IRF4 rearrangement
- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the central nervous system (CNS)
- Primary cutaneous DLBCL, leg type
- EBV+ DLBCL, NOS
- EBV+ mucocutaneous ulcer
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma

- ALK+ large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- HHV-8+ DLBCL, NOS
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

3.1.2 Patients must have measurable disease, defined as at least one lesion that is > 15 mm (1.5 cm) in the longest axis on cross-sectional imaging and measureable in two perpendicular dimensions per computed tomography (spiral CT), PET-CT or MRI.

3.1.3 Patients must have disease that has relapsed after or is refractory to at least 2 lines of standard therapy. The remaining standard treatment options are unlikely to be effective in the opinion of the treating physician, or patient is felt to be ineligible for such therapies or the patient refuses such therapies. Patients who have undergone autologous stem cell transplant are eligible as long as they meet all other criteria.

3.1.4 Age ≥ 18 years.
Because no dosing or adverse event data are currently available on the use of CDX-1127 (varlilumab) in combination with nivolumab in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.5 ECOG performance status of 0 or 1 (See Appendix A).

3.1.6 Life expectancy of greater than 12 weeks

3.1.7 Patients must have normal organ and marrow function as defined below within 14 days of registration:

- White blood cell (WBC) ≥ 2000/mm^3
- Absolute neutrophil count (ANC) ≥ 1500/mm^3
- Platelet count ≥ 100,000/mm^3
- Hemoglobin > 9.0 g/dL
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) (except patients with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)
- Aspartate transaminase (AST) ≤2.5 x ULN
- Calculated creatinine clearance (CrCl) ≥ 50 mL/min (if using the Cockcroft-Gault formula below):

$$\textit{Female}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\textit{Male}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg}}{72 \times \text{serum creatinine in mg/dL}}$$

3.1.8 Females of child bearing potential per protocol section 3.3 must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG)

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

3.2 Exclusion Criteria

3.2.1 Patient has received chemotherapy, targeted agent, or radiotherapy within 4 weeks or at least 5 half-lives, whichever is longer, prior to registration.

Palliative (limited-field) radiation therapy is permitted, if all of the following criteria are met:

1) Repeat imaging demonstrates no new sites of bone metastases.
2) The lesion being considered for palliative radiation is not a target lesion.

3.2.2 Patient has received immunotherapy (including monoclonal antibodies) within 4 weeks prior to registration.

3.2.3 Patients who have not recovered to grade 1 or less from any adverse events due to agents administered more than 4 weeks earlier (excluding alopecia)

3.2.4 Patients who are receiving any other investigational agents.

3.2.5 Patients should be excluded if they have had prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways.

3.2.6 Patients who have received autologous stem cell transplant (ASCT) ≤ 12 weeks prior to the first dose of study drug.

3.2.7 Patients with a prior history of allogeneic stem cell or solid organ transplantation.

3.2.8 Patients with evidence of active disease in the central nervous system (CNS) defined as either the presence of active lesions on MRI obtained within 4 weeks of registration or progressive neurological decline.

Patients with primary CNS lymphoma who develop systemic recurrence following standard therapy may be included as long as no active CNS disease is present at the time or enrollment. Similarly, patients with secondary involvement of the CNS from a systemic lymphoma may be included as long as the CNS disease has been optimally treated and they demonstrate no evidence of active CNS disease.

3.2.9 History of allergic reactions attributed to compounds of similar chemical or biologic composition to CDX-1127 (varlilumab) and/or nivolumab.

3.2.10 History of severe hypersensitivity reaction to any monoclonal antibody.

3.2.11 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.12 Pregnant women are excluded from this study because CDX-1127 (varlilumab) and nivolumab are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with CDX-1127 (varlilumab) or nivolumab, breastfeeding should be discontinued if the mother is treated with CDX-1127 (varlilumab) or nivolumab.

3.2.13 Patients with human immunodeficiency virus (HIV) are eligible for the study provided they meet the other protocol criteria in addition to the following:

- Undetectable HIV load by standard PCR clinical assay within 60 days prior to registration
- Absolute CD4 count of ≥ 200 mm^3 within 60 days prior to registration
- Willing to maintain adherence to combination antiretroviral therapy
- No history of AIDS defining condition (other than lymphoma or CD4 cell count < 200 mm^3)
- Likely to have near normal lifespan if not for the presence of relapsed/refractory lymphoma

Patients with evidence of HBV are eligible provided there is minimal hepatic injury and the patient has undetectable HBV on suppressive HBV therapy. Patient must be willing to maintain adherence to HBV therapy.

Patients with previously treated and eradicated HCV who have minimal hepatic injury are eligible.

3.2.14 Patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids, should be excluded. These include but are not limited to patients with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, connective tissue diseases, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome should be excluded because of the risk of recurrence or exacerbation of disease. Patients with vitiligo, endocrine deficiencies including thyroiditis managed with replacement hormones including physiologic corticosteroids are eligible. Patients with rheumatoid arthritis and other arthropathies, Sjögren's syndrome and psoriasis controlled with topical medication and patients with positive serology, such as antinuclear antibodies (ANA), anti-thyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible.

3.2.15 Patients are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger (precipitating event).

3.2.16 Patients should be excluded if they have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses $\leq$ 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. Patients are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if $\leq$ 10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (*e.g.*, contrast dye allergy) or for treatment of non-autoimmune conditions (*e.g.*, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

3.2.17 Patients who have had evidence of active or acute diverticulitis, intra-abdominal abscess, GI obstruction and abdominal carcinomatosis which are known risk factors for bowel perforation should be evaluated for the potential need for additional treatment before coming on study.

3.2.18 Patients with other active malignancy $\leq$ 3 years prior to registration for which active treatment is required must be excluded. Patients with composite lymphomas that have a non-B-cell component must be excluded.
EXCEPTIONS: Non-melanotic skin cancer or carcinoma-in-situ of the cervix

3.3 Females of Childbearing Potential

A female of child-bearing potential is defined as any female who has experienced

menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a female over 45 in the absence of other biological or physiological causes. In addition, females who meet clinical criteria for menopause but are under the age of 55 must have a documented serum follicle stimulating hormone (FSH) level higher than 40 mIU/mL.

The effects of CDX-1127 (varlilumab) and nivolumab on the developing human fetus are unknown. For this reason, and because the study drugs used in this trial are known to be teratogenic, females of child-bearing potential 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 for 23 weeks after the last dose of study drug. Males who are the sexual partners of a female of child-bearing potential must use any contraceptive method with a failure rate of less than 1% per year for the duration of study participation and for a period of 31 weeks after the last dose of study drug. These periods of required use of contraception have been calculated using the upper limit of the half-life for nivolumab (25 days) and are based on the protocol requirement that females of child-bearing potential use contraception for 5 half-lives plus 30 days and males who are the sexual partners of females of child-bearing potential use contraception for 5 half-lives plus 90 days.

Females who are not of childbearing potential (*i.e.*, who are postmenopausal or surgically sterile) and azoospermic males do not require contraception.

Should a female of child-bearing potential become pregnant or suspect she is pregnant while she or her partner is participating in this study, she (or the participating partner) should inform the treating physician immediately.

3.4 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

Both males and females of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require IND sponsors to select qualified investigators. NCI policy requires all persons participating in any NCI-sponsored clinical trial to register and renew their registration annually.. To register, all individuals must obtain a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN or RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

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

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

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

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

4.2 Site Registration

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

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

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

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

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

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

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the 10089 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP-IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or

- Click on the By Lead Organization folder to expand, then select LAO-MN026, and protocol # 10089.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Requirements For Protocol 10089 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- Site Initiation Visit

4.2.3 Submitting Regulatory Documents

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

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

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

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

4.2.4 Checking **Site** Registration Status

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

Go to https://www.ctsu.org and log into the members area using your CTEP-IAM username and password.
Click on the Regulatory tab at the top of your screen.
Click on the Site Registration subtab.
Enter your 5-character CTEP Institution Code and click on Go.
Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the

protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

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

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar.
- To access cohort management: Be identified to Theradex as the "Client Admin" for the study.
- Have regulatory approval for the conduct of the study at their site.

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

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form and HIPAA authorization form.

4.3.3 OPEN/IWRS Questions?

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

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. . This link to the Theradex website is also on the CTSU website OPEN tab.

For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 609-619-7862 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

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

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. The study drugs may be administered in sequence, without regard to order. Do not administer study drugs concurrently. For patients receiving both drugs, the intravenous catheter must be flushed with 0.9% sodium chloride between the two infusions. Pre-medication is not needed unless a patient develops an infusion reaction.

Patients will be randomly allocated for treatment in one of two groups (group 1 or group 2). Both groups will receive Nivolumab at the dose of 240 mg IV every 2 weeks for the first 4 months on the study. After four months, Nivolumab will be administered at the dose of 480 mg IV every 4 weeks. Patients allocated to group 2 will also receive CDX-1127 (varlilumab) at the dose of 3 mg/kg IV every 4 weeks. Response assessment will be performed every 12 weeks. Patients in group 1 (nivolumab alone) who meet criteria for disease progression at any point in the study will be allowed to cross-over to group 2 (nivolumab and CDX-1127 (varlilumab) and continue on the study. A repeat biopsy is mandatory for patients who wish to cross-over from group 1 to group 2 at the time of disease progression.

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

5.1.1 CDX-1127 (Varlilumab)

CDX-1127 (Varlilumab) will be given every four weeks ± 2 days at a dose of 3 mg/kg. Patients may be dosed no less than 26 days from the previous dose of drug.

CDX-1127 (Varlilumab) is to be administered as a 90-minute intravenous (IV) infusion

using a 0.2 – 0.22 micron in-line filter connected to the infusion set. CDX-1127 (Varlilumab) should not be administered as a bolus injection. All patients should be monitored for 4-6 hours following the first two doses and 2 hours following all subsequent doses; patients who experience any treatment-related adverse events during the observation period should be further monitored as clinically appropriate (*e.g.*, for up to 24 hours post-dose).

CDX-1127 (Varlilumab) cannot be mixed with any other drug in the infusion bag or the administration set.

5.1.2 Nivolumab

Nivolumab will be given every two weeks ± 2 days at a dose of 240 mg for 4 months followed by 480 mg every 4 weeks thereafter. Patients may be dosed no less than 12 days from the previous dose of drug during cycles 1 - 5 and no less than 26 days from the previous dose beginning with cycle 6.

There will be no dose modifications allowed.

Nivolumab is to be administered as a 30-minute IV infusion, using a volumetric pump with a 0.2-1.2 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for delivery but the total volume must not exceed 160 mL. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

5.2 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of CDX-1127 (varlilumab) and nivolumab with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. Appendix B, the Patient Wallet Card, will be given to patients to identify the study physician and provide a contact telephone number.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for up to a maximum of 2 years or until one of the following criteria applies:

- Disease progression (except patients on group 1 who wish to cross-over to group 2),
- Intercurrent illness that prevents further administration of treatment,
- Adverse event(s) which require(s) permanently going off study treatment (see also section 6 and specific algorithms in Appendix E)
- Any dosing interruption lasting > 6 weeks, with the following exceptions: Dosing

interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Principal Investigator must be consulted.

- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical deterioration as defined by acute or progressive decline in performance status, progressive debility or progressive increase in tumor-associated symptoms that negatively impact the patient's quality of life as judged by the treating physician.
- Patient non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation must be documented in the Case Report Form (CRF).

5.4 Duration of Follow Up Following End of Therapy

Patients will be followed for additional 100 days (based on 5 half-lives) after end of therapy or until death, whichever occurs first. Patients removed from therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.5 Criteria for Removal from Study

Patients treated in group 1 (Nivolumab alone) are allowed to cross-over to group 2 at the time of documented disease progression. A repeat biopsy is mandatory to confirm progressive disease. Patients who cross-over from group 1 to group 2 may continue treatment for an additional 2 years (counting from the start of treatment on group 2) as long as he or she does not meet other criteria for removal from the study.

Patients will be removed from study when any of the applicable criteria occur: completion of follow-up as described in Section 5.4 above, patient withdrawal, or

inability to follow study protocol as listed in Section 5.3. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

5.6 Criteria to Resume Treatment Following a Drug-Related Adverse Event

Some patients may continue to benefit from treatment, maintaining or improving responses after developing a drug-related adverse event that requires temporary discontinuation of the study drugs. These may include patient who require treatment with steroids.

Patients who develop drug-related adverse events may resume therapy only if he or she meets the dose modification criteria as described in the tables in Section 6.

If the criteria to resume treatment are met, the patient should restart treatment no sooner than the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol the treatment should resume at the earliest convenient point that is within the six week delay period.

For patients who develop immune-related adverse events, including those who require treatment with high dose steroids treatment may be resumed if all the following are met:

- Must resolve to baseline within 6 weeks of treatment
- Must be off steroids for at least 2 weeks with no recurrence or new events New immune related events or exacerbation of existing events during steroid treatment or taper suggest the presence of ongoing immune activation and should require permanent discontinuation of nivolumab.
- Must have had no recurrence of symptoms or new symptoms during steroid taper.

5.7 Treatment of Study Drug Related Infusion Reactions

Since nivolumab and CDX-1127 (varlilumab) contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, urticaria, angioedema, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE version 5.0 guidelines.

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

Remain at bedside and monitor subject until recovery from symptoms.

For Grade 1 symptoms (Mild transient reaction; infusion interruption not indicated; intervention not indicated):

Infusion rate may be slowed or interrupted and restarted at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely.

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional administrations of study drugs, slowing infusion rate as above.

If the grade 1 event occurs during the infusion of the first drug in patients randomized to the combination therapy arm (group 2), the second drug may still be given as long as the patient is closely monitored and there is no evidence of increase in severity of reaction (beyond grade 1).

For Grade 2 symptoms (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment [e.g., antihistamines, NSAIDS, narcotics, IV fluids]; prophylactic medications indicated for ≤24 hrs):

Stop the study drug infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor patient until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely. If symptoms recur, re administer diphenhydramine 50 mg IV, and remain at bedside and monitor the patient until resolution of symptoms. No further study drug will be administered in the setting of a recurrent infusion reaction and the amount of study drug infused must be recorded on the electronic case report form (eCRF).

Close observation for resolution of symptoms and supportive care may need to be continued 24-48 hours. If the event (i.e. recurrent infusion reaction) occurs during the infusion of the first drug in patients randomized to the combination therapy arm (group 2), the second drug will also be held for that day but may be administered the following day as long as infusion-related symptoms have resolved. Given the degree of clinical experience with nivolumab and its known low likelihood of infusion reaction we recommend that it be administered first for those patients in the combination therapy arm (Group 2).

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and (acetaminophen) (or paracetamol) 325 to

1000 mg should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms:

- **Grade 3 symptoms**: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae

- **Grade 4 symptoms:** Life-threatening consequences; urgent intervention indicated

Immediately discontinue infusion of the study drug. Begin an IV infusion of normal saline, and bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Patient should be monitored until the investigator is comfortable that the symptoms will not recur.

Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery from symptoms.

For Grade 4 infusion reactions, study drug(s) will be permanently discontinued.

Patients with Grade 3 infusion reactions who have not been pre-medicated may continue study treatment with appropriate pre-medication, at the discretion of the investigator. Recommended prophylactic pre-medications for all subsequent infusions as described in management of Grade 2 infusion reactions. Study drug(s) should be permanently discontinued for recurrence of Grade 3 infusion reaction for patients who have received pre-medications.

In the case of late-occurring hypersensitivity symptoms (*e.g.*, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (*e.g.*, oral antihistamine, or corticosteroids). Additional treatment prior to next dose as per guidelines above.

Please note that late occurring events including isolated fever and fatigue may represent the presentation of systemic inflammation. Please evaluate accordingly.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Dose Modifications for Group 1 (Nivolumab alone) and Group 2 (Nivolumab and CDX-1127 (Varlilumab)

Below are DOSE MODIFICATION tables applicable to all patients participating in this study for the following adverse events. This applies to all patients whether they have been assigned to Group 1 (nivolumab alone) or Group 2 (nivolumab and CDX-1127 (varlilumab)

Patients who develop adverse events while being treated with combinatory therapy CDX-1127 (varlilumab and nivolumab - Group 2 patients) must have both drugs held or discontinued according to the guidance provided in the tables below. Treatment with single-agent will not be permitted at any time for patients who are randomized to Group 2 and develop adverse events.

Please use as written and contact the drug monitor for any proposed changes. Note that if a patient experiences several adverse events and there are conflicting recommendations, the investigator should use the recommended treatment modification for the most serious event that has a higher level of modification, i.e. going off study treatment versus holding drug.

A patient who requires treatment to be held within the first 4 months on the study will continue to receive nivolumab at the dosage of 240 mg every 2 weeks if he meets criteria to resume treatment before the 4 months' timepoint. For this patient, the change in dosage and frequency of nivolumab (from 240 mg every 2 weeks to 480 mg every 4 weeks) should occur at the 4-month mark regardless of the number of nivolumab infusions received prior to holding treatment. However, if the same patient only meets criteria to resume treatment after the 4-month mark he or she will resume treatment with nivolumab 480 mg every 4 weeks regardless of the total number of nivolumab infusions received up to that point.

In several places there are differences between the protocol specific guidelines in Section 6.1 and the toxicity management algorithms in Appendix D. In these instances, the protocol specific guidelines should be followed. These treatment guidelines and management algorithms should be followed unless there are specific clinical circumstances for which the treating physician decides an alternative treatment approach is clinically appropriate. Consultation with the study PI or drug monitor is recommended.

Generally we strongly encourage early evaluation while withholding drug, and appropriate treatment as indicated in the management tables and event specific guidelines.

Dose hold = All study drugs must be held. Day 1 of the next cycle is given when the patient meets the protocol criteria to restart drugs. The current cycle will include all days until the patient resumes treatment and may be longer than 28 days.

ALL OTHER EVENTS	**Management/Next Dose**
≤ Grade 1	No change in dose

ALL OTHER EVENTS	**Management/Next Dose**
Grade 2	Hold until ≤ Grade 1 OR baseline (exceptions as noted below)
Grade 3	Off protocol therapy (exceptions as noted below)
Grade 4	Off protocol therapy
Recommended management: As clinically indicated	

- Any grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment should go off protocol treatment

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued study drug dosing should go off protocol treatment.

- Any grade 3 or 4 drug-related laboratory abnormality or electrolyte abnormality, that can be managed independently from underlying organ pathology with electrolyte replacement, hormone replacement, insulin or that does not require treatment **does not** require discontinuation.

- Lymphopenia is an expected event for both study drugs. Asymptomatic lymphopenia does not constitute reason to hold or discontinue the study drugs, regardless of the grade

Skin Rash and Oral Lesions	**Management/Next Dose**
≤ Grade 1	No change in dose *
Grade 2	Hold* until 1≤ Grade resolved. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Resume at same level at investigator discretion
Grade 4	Off protocol therapy
*Patients with purpuric or bullous lesions must be evaluated for vasculitis, Steven-Johnson syndrome, TEN, and autoimmune bullous disease including oral lesions of bullous pemphigus/pemphigoid. Pruritus may occur with or without skin rash and should be treated symptomatically if there is no associated liver or GI toxicity. Note skin rash typically occurs early and may be followed by additional events particularly during steroids tapering.	
Recommended management: AE management guidelines	

Liver Function AST, ALT, Bilirubin	**Management/Next Dose**

Liver Function AST, ALT, Bilirubin	**Management/Next Dose**
≤ Grade 1	Hold until UNL or baseline. Resume at same dose level.
Grade 2	Hold until UNL or baseline. Resume at same dose level.
Grade 3	Off protocol therapy
Grade 4	Off protocol therapy
Continued treatment of active immune mediated hepatitis may exacerbate ongoing inflammation. Holding drug to evaluate LFT changes and early treatment are recommended. LFT changes may occur during steroid tapers from other events and may occur together with other GI events including cholecystitis/pancreatitis.	
Recommended management: see Hepatic AE management algorithm	

Diarrhea/ Colitis	**Management/Next Dose**
≤ Grade 1	Hold until baseline. No change in dose
Grade 2	Hold until baseline. No change in dose
Grade 3	Off protocol therapy.
Grade 4	Off protocol therapy
See GI AE Algorithm for management of symptomatic colitis. Patients with grade 2 symptoms but normal colonoscopy and biopsies may be retreated after resolution. Patients who require steroids should be taken off study treatment. Please evaluate pituitary function prior to starting steroids if possible without compromising acute care. Evaluation for all patients for additional causes includes *C. diff*, acute and self-limited infectious and foodborne illness, ischemic bowel, diverticulitis, and IBD.	
Recommended management: see GI AE management Algorithm	

Pancreatitis Amylase/Lipase	**Management/Next Dose**
≤ Grade 1	Hold dose until baseline. Resume at same dose level if asymptomatic
Grade 2	Hold until baseline. Resume at same dose level if asymptomatic
Grade 3	Hold until baseline. Resume at same dose level if asymptomatic. Patients who develop symptomatic pancreatitis or DM should be taken off treatment
Grade 4	Hold until baseline. Resume at same dose level if asymptomatic. Patients who develop symptomatic pancreatitis or DM should be taken off treatment
Patients may develop symptomatic and radiologic evidence of pancreatitis as well as DM and DKA. Lipase elevation may occur during the period of steroid withdrawal and with other immune mediated events or associated with colitis, hepatitis, and patients who have asymptomatic lipase elevation typically have self-limited course and may be retreated. For treatment management of symptomatic pancreatitis please follow the Hepatic Adverse Event Management Algorithm	

Pneumonitis	**Management/Next Dose**

Pneumonitis	**Management/Next Dose**
≤ Grade 1	Hold dose pending evaluation and resolution to baseline including baseline pO2. Resume no change in dose after pulmonary and/or ID consultation excludes lymphocytic pneumonitis.
Grade 2	Hold dose pending evaluation. Off protocol therapy if steroids are required.
Grade 3	Hold dose pending evaluation. Off protocol therapy if steroids are required
Grade 4	Off protocol therapy
Distinguishing inflammatory pneumonitis is often a diagnosis of exclusion for patients who do not respond to antibiotics and have no causal organism identified including influenza. Most patients with respiratory failure or hypoxia will be treated with steroids. Bronchoscopy may be required and analysis of lavage fluid for lymphocytic predominance may be helpful. Patients with new lung nodules should be evaluated for sarcoid like granuloma. Please consider recommending seasonal influenza killed vaccine for all patients.	
Recommended management: See Pulmonary Adverse Event Management Algorithm	

Other GI (not Nausea and Vomiting)	**Management/Next Dose**
≤ Grade 1	No change in dose.
Grade 2	Hold pending evaluation for gastritis duodenitis and other immune adverse events or other causes. Resume at same dose level after resolution to ≤ Grade 1.
Grade 3	Hold pending evaluation until ≤ Grade 1. Resume at same dose level. If symptoms do not resolve within 7 days with symptomatic treatment patients should go off protocol therapy
Grade 4	Off protocol therapy
Patients with grade 2 or 3 N-V should be evaluated for upper GI inflammation and other immune related events.	

Fatigue	**Management/Next Dose**
≤ Grade 1	No change in dose.
Grade 2	No change in dose
Grade 3	Hold until ≤ Grade 2. Resume at same dose level
Fatigue is the most common adverse event associated with immune checkpoint therapy. Grade 2 or greater fatigue should be evaluated for associated or underlying organ involvement including pituitary, thyroid, and hepatic, or muscle (CPK) inflammation	

Neurologic events	**Management/Next Dose**
≤ Grade 1	Hold dose pending evaluation and observation. Resume with no change in dose when resolved to baseline. .
Grade 2	Hold dose pending evaluation and observation. Hold until ≤ Grade 1. Off protocol therapy if treatment with steroids is required. Resume at

Neurologic events	**Management/Next Dose**
	same dose level for peripheral isolated n. VII (Bell's palsy)^
Grade 3	Off protocol therapy
Grade 4	Off protocol therapy
Patients with any CNS events including aseptic meningitis, encephalitis, symptomatic hypophysitis, or myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome and myasthenia gravis should be off study.	
Recommended management: See Neurologic Adverse Event Management Algorithm	

Endocrine Hypophysitis Adrenal Insufficiency	**Management/Next Dose**
≤ Grade 1	Asymptomatic TSH elevation * Hold pending evaluation, endocrine consult
Grade 2	Hold until patients are on a stable replacement hormone regimen. If treated with steroids patients must be stable off steroids for two weeks. Resume at same dose level.
Grade 3	Off study treatment.
Grade 4	Off protocol therapy
Note all patients with symptomatic pituitary enlargement, exclusive of hormone deficiency, but including severe headache or enlarged pituitary on MRI should be considered grade 3 events. Isolated thyroid or testosterone deficiency may be treated as grade 2 if there are no other associated deficiencies and adrenal function is monitored. Please evaluate pituitary function before beginning steroid therapy or replacement therapy of any kind. *Note patients with thyroiditis may be retreated on replacement therapy. Patients must be evaluated to rule out pituitary disease prior to initiating thyroid replacement.	
Recommended management: See Endocrine Management Algorithm	

Creatinine Increased	**Management/Next Dose**
≤ Grade 1	No change in dose. Monitor toxicity weekly until returned to baseline.
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Off treatment
Recommended management: See Renal Management Algorithm	

Infusion Reaction	**Management/Next Dose**
≤ Grade 1	Infusion may be slowed or interrupted until symptoms resolve. See Section 5.7 for details on management and subsequent dosing.
Grade 2	Interrupt until symptoms resolve. See Section 5.7 for details on

Infusion Reaction	**Management/Next Dose**
	management and subsequent dosing.
Grade 3	Immediately discontinue infusion. See Section 5.7 for details on management and subsequent dosing.
Grade 4	Immediately discontinue infusion. See Section 5.7 for details on management. Permanently discontinue study drug(s).
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever	

Fever	**Management/Next Dose**
≤ Grade 1	Evaluate and continue at same dose level
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Off treatment
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever	
See section 5. infusion reactions	

Cardiac *	**Management/Next Dose for Cardiac Toxicities**
≤ Grade 1	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize may resume therapy. If labs worsen or symptoms develop then treat as below. Hold pending evaluation
Grade ≥2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone. If no improvement within 24 hours, add either infliximab, ATG or tacrolimus. Consult algorithm for more details. Resume therapy if there is a return to baseline and myocarditis is excluded or considered unrelated.
Grade ≥2 with confirmed myocarditis	Off protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone Add ATG or tacrolimus if no improvement. Off treatment.
* Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin **Patients with evidence of myositis without myocarditis may be treated according as "other event" Note: The optimal treatment regimen for immune mediated myocarditis has not been	

established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.

- Drug will be held for grade 2 cardiac dysfunction pending evaluation
- Drug will be permanently discontinued for grade 3 or 4 cardiac dysfunction and grade 2 events that do not recover to baseline or that reoccur
- Treatment with steroids as clinically indicated

If treatment is delayed > 6 weeks for an adverse event, the patient must be permanently discontinued from study therapy.

Patients requiring high dose steroid treatment for autoimmune or inflammatory events should go off study treatment except for a short course of tapering steroids for infusion reaction, skin rash or endocrine events.

Patients with grade 3 thyroiditis and skin rash may continue therapy with resolution and stable replacement treatment.

Patients with thyroiditis or hypopituitarism who are stable as above may be restarted with replacement hormones including thyroid hormone and physiologic doses of corticosteroids.
Please note that grading and for hypophysitis with symptoms of headache, visual or neurologic changes or radiologic evidence of pituitary enlargement and other CNS events such as aseptic meningitis or encephalitis should be considered grade 3 events.
Any patients who require additional immune suppressive treatment beyond steroids should go off study treatment

Patients requiring > two dose delays for the same event should go off protocol therapy.

Prior to starting corticosteroids or hormone replacement for any reason, appropriate endocrine testing including cortisol, ACTH, TSH and T4 must be obtained to document baseline.

Please note that in some cases the treatment algorithms recommend steroids if symptoms do not resolve in 7 days. However, this recommendation is not meant to delay steroid treatment at any time it is clinically indicated.

Patients may be dose-delayed for evaluation and restarted depending on results.
Any patient started on corticosteroids initially who is determined to not require steroid treatment for an autoimmune adverse event may resume therapy after a 2 week observation period without further symptoms at the discretion of the PI or investigator.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Sections 7.2 and 7.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) in addition to routine reporting.

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

7.1.1 CAEPRs for CTEP IND Agent(s)

7.1.1.1 CAEPR for CDX-1127 (Varlilumab)

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
CDX-1127 (Varlilumab, NSC 778372)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 343 patients.* Below is the CAEPR for CDX-1127 (varlilumab).

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

Version 2.1, September 14, 2019[1]

Adverse Events with Possible Relationship to CDX-1127 (varlilumab) (CTCAE 5.0 Term) [n= 343]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
CARDIAC DISORDERS			
		Pericardial effusion	
ENDOCRINE DISORDERS			
		Hyperthyroidism	
	Hypothyroidism		
EYE DISORDERS			
		Blurred vision	
		Dry eye	
		Eye disorders - Other (transient central vision loss)	

Adverse Events with Possible Relationship to CDX-1127 (varlilumab) (CTCAE 5.0 Term) [n= 343]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Eye disorders - Other (visual acuity reduced transiently)	
		Floaters	
		Watering eyes	
GASTROINTESTINAL DISORDERS			
		Colitis	
	Diarrhea		***Diarrhea (Gr 2)***
	Nausea		***Nausea (Gr 2)***
		Proctitis	
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
Fatigue			***Fatigue (Gr 2)***
	Fever		
	Flu like symptoms		
	Malaise		
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (hepatitis)	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
		Cytokine release syndrome[2]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		
INVESTIGATIONS			
	Alanine aminotransferase increased[3]		
	Alkaline phosphatase increased[3]		
	Aspartate aminotransferase increased		
	Blood bilirubin increased[3]		
	GGT increased[3]		
	Lipase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Neutrophil count decreased		
	Serum amylase increased		
	Thyroid stimulating hormone increased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Tumor lysis syndrome[4]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
NERVOUS SYSTEM DISORDERS			
	Headache		

Adverse Events with Possible Relationship to CDX-1127 (varlilumab) (CTCAE 5.0 Term) [n= 343]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Nervous system disorders - Other (peripheral sensorimotor neuropathy)	
		Paresthesia	
		Peripheral sensory neuropathy	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Pruritus			***Pruritus (Gr 2)***
Rash maculo-papular			***Rash maculo-papular (Gr 2)***
		Skin hyperpigmentation	
		Skin hypopigmentation	

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

[2]Symptoms of cytokine release syndrome (CRS) and/or allergic reaction may include chills, fever, fatigue, flushing, bronchospasm, and hypotension. In some cases, disseminated intravascular coagulation (DIC), capillary leak syndrome (CLS), and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) have been reported in the setting of CRS.

[3]Symptoms of hepatic dysfunction may include Alanine aminotransferase increased, Alkaline phosphatase increased, Aspartate aminotransferase increased, Blood bilirubin increased, and GGT increased under the INVESTGATIONS SOC.

[4]Tumor lysis syndrome is defined as a massive overload of potassium, phosphate, uric acid, plus hypocalcemia, potentially causing lethal cardiac arrhythmias and/or renal failure.

NOTE: Adverse reactions generally low grade that may represent immune-mediated toxicity, such as rash, diarrhea, fever, and increased liver function tests, have been observed in patients receiving CDX-1127 monotherapy and may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of CDX-1127, administration of corticosteroids and supportive care. Immune-related adverse events which are expected with checkpoint inhibition, have been observed among the patients who have received CDX-1127 (varlilumab) in combination with checkpoint inhibitors.

Adverse events reported on CDX-1127 (varlilumab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that CDX-1127 (varlilumab) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis; Lymph node pain
CARDIAC DISORDERS - Sinus tachycardia
GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Constipation; Dry mouth; Dyspepsia; Dysphagia; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other

(tongue discoloration); Gastrointestinal disorders - Other (tongue ulceration); Gastrointestinal pain; Lower gastrointestinal hemorrhage; Mucositis oral; Oral dysesthesia; Oral pain; Periodontal disease; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Gait disturbance; General disorders and administration site conditions - Other (temperature intolerance); Localized edema; Non-cardiac chest pain; Pain
INFECTIONS AND INFESTATIONS - Appendicitis; Infections and infestations - Other (candida infection); Infections and infestations - Other (epididymitis); Infections and infestations - Other (Herpes zoster); Mucosal infection; Sepsis; Sinusitis; Thrush
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Injury, poisoning and procedural complications - Other (procedural pain)
INVESTIGATIONS - Creatinine increased; Investigations - Other (haptoglobin increased); Investigations - Other (urobilinogen urine increased); Platelet count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (cachexia); Metabolism and nutrition disorders - Other (hyperalbuminemia); Metabolism and nutrition disorders - Other (malnutrition)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Flank pain; Generalized muscle weakness; Muscle cramp; Musculoskeletal and connective tissue disorder - Other (axillary pain); Musculoskeletal and connective tissue disorder - Other (groin pain); Musculoskeletal and connective tissue disorder - Other (osteolysis); Musculoskeletal and connective tissue disorder - Other (pain in jaw); Myalgia; Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Dizziness; Dysgeusia; Lethargy
PSYCHIATRIC DISORDERS - Insomnia; Irritability; Personality change
RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Hematuria; Renal and urinary disorders - Other (urine odor abnormal); Urinary frequency
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Bronchopulmonary hemorrhage; Bronchospasm; Cough; Dyspnea; Nasal congestion; Oropharyngeal pain; Respiratory failure; Sinus pain; Sneezing; Voice alteration; Wheezing
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Bullous dermatitis; Dry skin; Erythroderma; Hyperhidrosis; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Rash acneiform; Skin and subcutaneous tissue disorders - Other (pemphigoid); Skin and subcutaneous tissue disorders - Other (skin hemorrhage)
VASCULAR DISORDERS - Flushing; Hot flashes; Hypertension; Hypotension

Note: CDX-1127 (varlilumab) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.1.2 CAEPR for Nivolumab

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Nivolumab (NSC 748726)

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

for further clarification. *Frequency is provided based on 2069 patients.* Below is the CAEPR for Nivolumab.

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

Version 2.4, December 2, 2020[1]

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Myocarditis	
		Pericardial tamponade[2]	
		Pericarditis	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[3]		
	Hyperthyroidism[3]		
	Hypophysitis[3]		
	Hypothyroidism[3]		
EYE DISORDERS			
		Blurred vision	
		Dry eye	
		Eye disorders - Other (diplopia)[3]	
		Eye disorders - Other (Graves ophthalmopathy)[3]	
		Eye disorders - Other (optic neuritis retrobulbar)[3]	
		Eye disorders - Other (Vogt-Koyanagi-Harada)	
	Uveitis		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis[3]		
		Colonic perforation[3]	
	Diarrhea		***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
		Enterocolitis	
		Gastritis	
		Mucositis oral	
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[4]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Injection site reaction		***Injection site reaction (Gr 2)***

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (immune-mediated hepatitis)	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[3]	
		Autoimmune disorder[3]	
		Cytokine release syndrome[5]	
		Immune system disorders - Other (GVHD in the setting of allotransplant)[3,6]	
		Immune system disorders - Other (sarcoidosis)[3]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[7]		
INVESTIGATIONS			
	Alanine aminotransferase increased[3]		***Alanine aminotransferase increased[3] (Gr 3)***
	Aspartate aminotransferase increased[3]		***Aspartate aminotransferase increased[3] (Gr 3)***
	Blood bilirubin increased[3]		***Blood bilirubin increased[3] (Gr 2)***
	CD4 lymphocytes decreased		***CD4 lymphocyte decreased (Gr 4)***
	Creatinine increased		
	Lipase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		
	Platelet count decreased		
	Serum amylase increased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Hyperglycemia	***Hyperglycemia (Gr 2)***
		Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis)[3]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Musculoskeletal and connective tissue disorder - Other (polymyositis)	
		Myositis	
		Rhabdomyolysis	
NERVOUS SYSTEM DISORDERS			
		Encephalopathy[3]	
		Facial nerve disorder[3]	
		Guillain-Barre syndrome[3]	
		Myasthenia gravis[3]	

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Nervous system disorders - Other (demyelination myasthenic syndrome)	
		Nervous system disorders - Other (encephalitis)[3]	
		Nervous system disorders - Other (meningoencephalitis)	
		Nervous system disorders - Other (meningoradiculitis)[3]	
		Nervous system disorders - Other (myasthenic syndrome)	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
		Reversible posterior leukoencephalopathy syndrome[3]	
RENAL AND URINARY DISORDERS			
		Acute kidney injury[3]	
		Renal and urinary disorders - Other (immune-mediated nephritis)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleural effusion[3]		
	Pneumonitis[3]		
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)[3]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme[3]	
	Pruritus[3]		***Pruritus[3] (Gr 2)***
	Rash maculo-papular[3]		***Rash maculo-papular[3] (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (bullous pemphigoid)	
	Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)[3]		
	Skin hypopigmentation[3]		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

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

[2]Pericardial tamponade may be related to possible inflammatory reaction at tumor site.

[3]Nivolumab being a member of class of agents involved in the inhibition of “immune checkpoints”, may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune thyroiditis, bullous pemphigoid, exacerbation of Churg-Strauss Syndrome, drug rash with eosinophilia systemic symptoms [DRESS] syndrome, facial nerve disorder (facial nerve paralysis), limbic encephalitis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, thyrotoxicosis, and adrenal insufficiency), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome.

[4]Pancreatitis may result in increased serum amylase and/or more frequently lipase.

[5]Cytokine release syndrome may manifest as hemophagocytic lymphohistiocytosis with accompanying fever and pancytopenia.

[6]Complications including hyperacute graft-versus-host disease (GVHD), some fatal, have occurred in patients receiving allo stem cell transplant (SCT) after receiving Nivolumab. These complications may occur despite intervening therapy between receiving Nivolumab and allo-SCT.

[7]Infusion reactions, including high-grade hypersensitivity reactions which have been observed following administration of nivolumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of nivolumab.

Adverse events reported on Nivolumab trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Nivolumab caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Heart failure; Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS - Vestibular disorder
EYE DISORDERS - Eye disorders - Other (iridocyclitis); Optic nerve disorder; Periorbital edema
GASTROINTESTINAL DISORDERS - Constipation; Duodenal ulcer; Flatulence; Gastrointestinal disorders - Other (mouth sores); Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Pain
HEPATOBILIARY DISORDERS - Bile duct stenosis
IMMUNE SYSTEM DISORDERS - Anaphylaxis; Immune system disorders - Other (autoimmune thrombotic microangiopathy); Immune system disorders - Other (limbic encephalitis)
INFECTIONS AND INFESTATIONS - Bronchial infection; Lung infection; Sepsis; Upper respiratory infection
INVESTIGATIONS - Blood lactate dehydrogenase increased; GGT increased; Investigations - Other (protein total decreased); Lymphocyte count increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Histiocytic necrotizing lymphadenitis)
NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Intracranial hemorrhage
PSYCHIATRIC DISORDERS - Insomnia
RENAL AND URINARY DISORDERS - Hematuria; Renal and urinary disorders - Other (tubulointerstitial

nephritis)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchospasm; Cough; Dyspnea; Hypoxia
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Pain of skin; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (rosacea)
VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Vasculitis

Note: Nivolumab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 Adverse Event Characteristics

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

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

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

Although standard AE attributions will be collected and recorded as part of this study all adverse events will be considered relevant to study treatment unless clearly determined to be unrelated to the drugs and therefore classified as unrelated.

7.3 Expedited Adverse Event Reporting

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

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

7.3.2 Distribution of Adverse Event Reports

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

7.3.3 Expedited Reporting Guidelines

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

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

"Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

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

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

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

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

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

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

Expedited AE reporting timelines are defined as:

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

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

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

7.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

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

CTCAE SOC	Adverse Event	CTCAE Grade at which the event will not require expedited reporting[1]
Investigations	Neutrophil count decreased	≤ Grade 4
	Platelet count decreased	≤ Grade 4
	White blood count	≤ Grade 4
	Lymphocyte count decreased	≤ Grade 4
Blood and lymphatic system disorders	Anemia	≤ Grade 4

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Hospitalization, or other serious outcomes, for signs and symptoms of progression of the cancer.

7.4 Routine Adverse Event Reporting

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

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

7.5 Secondary Malignancy

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

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

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

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.6 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

8. PHARMACEUTICAL INFORMATION

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

8.1 CTEP IND Agent(s)

8.1.1 CDX-1127 (Varlilumab; NSC 778372)

Other Names: CDX-1127 (Varlilumab)

Classification: monoclonal antibody of the IgG1κ isotope

M.W.: 146,076 Dalton

Mode of Action: CDX-1127 (Varlilumab) binds to human CD27 and acts as an agonist of CD27, reacting with the ligand binding site of CD27 as demonstrated by inhibition of CD70 binding to CD27. CDX-1127 (Varlilumab) does not bind other tumor necrosis factor receptor (TNFR) family members. CDX-1127 (Varlilumab) does not lead to direct activation of lymphocytes in the absence of signaling through the T cell receptor (TCR).

Description: CDX-1127 (Varlilumab) is a recombinant, fully human monoclonal antibody (mAb) of the IgG1κ isotype that specifically binds human CD27. The amino acid sequence of CDX-1127 (varlilumab) has been determined and its structure is comprised of two IgG1 heavy chains and two kappa light chains which are disulfide-linked as expected for a mAb.

How Supplied: CDX-1127 (Varlilumab) is formulated as a clear, colorless, sterile solution intended for single-use parenteral administration. Each vial contains a nominal 50 mg CDX-1127 (varlilumab) protein in a 10.0 mL volume of buffered solution composed of Sodium Phosphate, Potassium Phosphate, Potassium Chloride, Sodium Chloride, and Polysorbate 80 with a pH of 7.0.

Preparation: Withdraw the prescribed dose of CDX-1127 (varlilumab) from the required number of vials. CDX-1127 (varlilumab) may be added to empty non-PVC/non-DEHP or PVC IV bags and administered undiluted or further diluted with 0.9% sodium chloride in a non-PVC/non-DEHP IV bag to a concentration between 0.27 mg/mL and 5 mg/mL or a PVC IV bag to a concentration between 0.1 mg/mL and 5 mg/mL. Gently invert the infusion bag 5 times to thoroughly mix the CDX-1127 (varlilumab) and 0.9% sodium chloride.

Storage: Store at 2 - 8°C (36 - 46°F). CDX-1127 (Varlilumab) should be protected from light. However, sufficient light protection is provided by the secondary container (carton); no specific light protection is needed during preparation of the dosing solution and infusion.

If a storage temperature excursion is identified, promptly return CDX-1127 (varlilumab) to 2 - 8°C (36 - 46°F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability studies are ongoing.

CAUTION: Once the sterile vials are entered (i.e., once CDX-1127 (varlilumab) is drawn into a syringe), the drug should be used as soon as possible (typically within 3 hours if kept at room temperature or within 6 hours if refrigerated; or in accordance with any applicable institutional guidance).

Route(s) **of Administration:** IV

Method of Administration: Infuse CDX-1127 (varlilumab) intravenously over 90 minutes using a polyethylene- or polypropylene-lined, non-DEHP-containing, low-protein binding/low-sorbing administration set with a 0.2 or 0.22 micron polyethersulfone (PES) in-line filter.

Patient Care Implications: It is possible that CDX-1127 (varlilumab) may exacerbate autoimmune diseases. Therefore, with the exception of vitiligo, CDX-1127 (varlilumab) should not be administered to patients with autoimmune diseases.

Management of CDX-1127(varlilumab) induced irAEs, should they occur, should be based on the extensive experience with treatment of toxicities related to ipilimumab and other checkpoint blockers. Guidelines and algorithms have been published for treatment of ipilimumab related toxicity (see ipilimumab package insert) and investigators should be familiar with these recommendations in the event of CDX-1127 induced irAEs (Di Giacomo, Biagioli et al. 2010; Kaehler, Piel et al. 2010).

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

Varlilumab is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.4).

8.1.2 Nivolumab (NSC 748726)

Amino Acid Sequence: 4 polypeptide chains, which include 2 identical heavy chains with 440 amino acids and 2 identical light chains.

Other Names: BMS-936558, MDX1106

Classification: Anti-PD-1MAb

M.W.: 146,221 Daltons

Mode of Action: Nivolumab targets the programmed death–1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor. PD-1 is a negative regulatory receptor expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligand 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Nivolumab inhibits the binding of PD-1 to PD-L1 and PD-L2. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens.

Description: Nivolumab Injection is a clear to opalescent, colorless to pale yellow

liquid; light (few) particulates may be present. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated in sodium citrate dihydrate, sodium chloride, mannitol, diethylenetriamine pentacetic acid (pentetic acid) and polysorbate 80 (Tween® 80), and water for injection. Dilute solutions of hydrochloric acid and/or sodium hydroxide may be used for pH adjustment (pH 5.5-6.5)..

How Supplied: Nivolumab is supplied by Bristol-Myers Squibb and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as 100 mg vials (10 mg/mL) with a 0.7 mL overfill. It is supplied in 10 mL type I flint glass vials, with fluoropolymer film-laminated rubber stoppers and aluminum seals.

Preparation: Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose, USP. When the dose is based on patient weight (i.e., mg/kg), nivolumab injection can be infused undiluted or diluted to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (eg, 240 mg, 360 mg, or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL. For patients weighing less than 40 kilograms (kg), the total
volume of infusion must not exceed 4 mL per kg of patient weight. During drug product preparation and handling, vigorous mixing or shaking is to be avoided.

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

Storage: Vials of Nivolumab injection must be stored at 2°-8°C (36°-46°F) and protected from light, freezing, and shaking. The unopened vials can be stored at room temperature (up to 25°C, 77°F) and room light for up to 48 hours. If a storage temperature excursion is identified, promptly return Nivolumab to 2°C-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

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

The administration of undiluted and diluted solutions of Nivolumab must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 24 hours in a refrigerator at 2°-8°C (36°-46°F) and a maximum of 8 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and room light. The maximum -8 hour period under room temperature and room light conditions includes the product administration period.

CAUTION: The single-use dosage form contains no antibacterial preservative or bacteriostatic agent. Therefore, it is advised that the product be discarded 8 hours after initial entry.

Route of Administration: Intravenous infusion over 30 minutes. Do not administer as

an IV push or bolus injection.

Method of Administration: Administer through a 0.2 micron to 1.2 micron pore size, low-protein binding polyethersulfone membrane in-line filter. Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

Potential Drug Interactions: None have been reported.

Potential Drug Interactions: The indirect drug-drug interaction potential of nivolumab was assessed using systemic cytokine modulation data for cytokines known to modulate CYP enzymes. There were no meaningful changes in cytokines known to have indirect effects on CYP enzymes across all dose levels of nivolumab. This lack of cytokine modulation suggests that nivolumab has no or low potential for modulating CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction.

Patient Care Implications: Women of childbearing potential (WOCBP) receiving nivolumab must continue contraception for a period of 5 months after the last dose of nivolumab. Men receiving nivolumab and who are sexually active with WOCBP must continue contraception for a period of 7 months after the last dose of nivolumab.

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

Nivolumab is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.4).

8.1.3 Agent Ordering and Agent Accountability

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

Supplies may be ordered once a patient has been enrolled to the study; starter supplies of investigational agents are not available.

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

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

8.1.3.3 Investigator Brochures - The current versions of the IBs for PMB-supplied agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via email.

8.1.3.4 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://eapps-ctep.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)
- IB Coordinator: ibcoordinator@mail.nih.gov

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Specimen Requirements for Correlative Studies

In this study, we propose several correlative studies, as detailed below. These assays are

specifically chosen to provide information on the status of the immune system in general as well as specific information related to the mechanism of action of the study drugs. One integrated biomarker study (CD27 by IHC) has been included which has been approved by the Biomarker Review Committee (BRC) of the Cancer Therapy Evaluation Program (CTEP). All other correlative studies will be exploratory in nature. Although exploratory, the proposed studies will be done on specimens obtained at time points relevant to standard clinical practice (prior to treatment, and at the time of suspected progression) in order to avoid unnecessary risks. The scientific information obtained from these studies is intended to be hypothesis-generating and will help us advance our understanding of the anti-tumoral immune system in the context of simultaneous manipulations using immunomodulatory drugs in lymphoma.

Submission of tumor tissue obtained from a biopsy performed within 60 days of registration is a mandatory part of this protocol. This tissue will be used to confirm the diagnosis and correctly stratify patients between categories A or B (Section 3.1.1). Submission of tumor tissue obtained from a biopsy performed to at the time of suspected disease progression is optional, except for Group 1 patients who cross over to Group 2, for these patients, the biopsy is mandatory. The importance of a repeat biopsy for patients in Group 1 who are suspected to have progressive disease is explained by the fact that responses to immunotherapy drugs may differ from those of standard cytotoxic treatments. Before proceeding with additional therapy we must exclude pseudo-progression and delayed responses by obtaining a repeat biopsy.

The biopsies obtained at the time of progression for patients in Group 2 or for those in Group 1 not wishing to cross-over to Group 2 are exploratory in nature. We anticipate that these biopsies will be done in approximately 25% of patients (some for this study and some also for eligibility in subsequent trials). Even though the cohort may be small, we may potentially gain insights into whether patients progress despite increased immune cell infiltration into the tumor.

All tumor biopsy tissue will be submitted in formalin-fixed paraffin-embedded (FFPE) format to the Mayo Clinic where biomarker specimen processing will be centralized. Once the quality of the specimen is verified by expert hematopathologist, ten 4 micron unstained slides will be forwarded to Mosaic Laboratories (Lake Forest, CA) for CD27 IHC assay (integrated biomarker). The remaining tissue block or slides will be used to generate specimens for exploratory biomarker studies including (1) additional unstained slides for IHC evaluation of intra-tumoral immune cells, (2) extraction of tumor DNA for whole-exome sequencing, (3) evaluation of 9p24.1 locus by FISH and (4) mass cytometry analysis of intra-tumoral immune cells all of which will be performed centrally at Mayo Clinic.

Serial collection of peripheral blood is also mandatory for patients participating in this study. Peripheral blood will be collected at baseline and every 14 days (prior to administration of study drugs) for the first 12 weeks on study. Submission of peripheral blood obtained at the time of disease progression is optional. Peripheral blood will be used to generate serum for cytokine profiling, isolation of peripheral blood mononuclear

cells for immunophenotyping, immunogenicity assays and pharmacokinetic studies.

Any surplus of tissue, DNA, cells or serum will be banked at Mayo Clinic for additional studies for the patients who provide additional consent for tissue banking. If consent for banking was not provided by the patient, the remaining blocks or slides will be returned to the original institution after minimum specimens are generated. Surplus of blood, plasma, serum, DNA and cells will be discarded once the minimum specimens are generated if the patient did not provide consent for banking of specimens.

Integrated Correlative Study

Correlative Study	Optional or Mandatory	Required Specimen	Collection Timepoints
Quantification/ Characterization of CD27+ cells by IHC	Mandatory	FFPE blocks (preferred) or 3 unstained glass slides with 4-micron-thick sections from FFPE blocks	***For all patients:*** Baseline (Within 60 days of registration)
	Mandatory	FFPE blocks (preferred) or 3 unstained glass slides with 4-micron-thick sections from FFPE	***For patients who cross over from Group 1 to Group 2 only:*** At the time of progression
	Optional	FFPE blocks (preferred) or 3 unstained glass slides with 4-micron-thick sections from FFPE	At the end of study (for all patients)

Exploratory Correlative Studies

Correlative Study	Optional or Mandatory	Required Specimen	Collection Timepoints
Analysis of Peripheral Blood Immune Cells by Mass Cytometry (CyTOF)[1]	Mandatory	Peripheral blood 12 mL collected in yellow top tubes (ACD)	Baseline and every 14 days for the first 12 weeks of treatment

Identification/ Characterization of Intratumoral Immune Cells by IHC and CyTOF	Mandatory	FFPE blocks (preferred) or 7 unstained glass slides with 4-micron-thick sections from FFPE	***For all patients:*** Baseline (Within 60 days of registration)
	Mandatory	FFPE blocks (preferred) or 7 unstained glass slides with 4-micron-thick sections from FFPE	***For patients who cross over from Group 1 to Group 2 only:*** At the time of progression
	Optional	FFPE blocks (preferred) or 7 unstained glass slides with 4-micron-thick sections from FFPE	***For all patients:*** At the end of study
Evaluation of Genetic Alterations of Chromosome 9p24.1 by FISH	Mandatory	FFPE blocks (preferred) or 1 unstained glass slide with 4-micron-thick section from FFPE	***For all patients:*** Baseline (Within 60 days of registration)
	Mandatory	FFPE blocks (preferred) or 1 unstained glass slides with 4-micron-thick section from FFPE	***For patients who cross over from Group 1 to Group 2 only:*** At the time of progression
	Optional	FFPE blocks (preferred) or 1 unstained glass slide with 4-micron-thick sections from FFPE	***For all patients:*** At the time of disease progression
Evaluation of Serum Cytokine Profile by ELISA[1]	Mandatory	10 mL peripheral blood collected in red top tubes (no anticoagulant)	Baseline and every 14 days for the first 12 weeks of treatment

Evaluation of pharmacokinetics and immunogenicity to CDX-1127 (Varlilumab)[1]	Mandatory	10 mL peripheral blood collected in red top tubes (no anticoagulant)	***Group 2:*** Baseline, pre-dose every 4 weeks for the first 4 cycles, at the end of treatment, and at safety follow-up (if available). ***Group 1:*** Baseline for all patients. ***Group 1 at cross-over:*** pre-dose every 4 weeks prior to the first 4 doses of CDX-1127 (varlilumab), at the end of treatment, and at safety follow-up (if available).
Evaluation of pharmacokinetics and immunogenicity to nivolumab[1]	Mandatory	10 mL peripheral blood collected in red top tubes (no anticoagulant)	***For all patients:*** Baseline, pre-dose every 4 weeks for the first 4 cycles, at the end of treatment, and at safety follow-up (if available).
Evaluation of Mutation Burden by WES	Mandatory	FFPE blocks (preferred) or 2 unstained glass slides with 4-micron-thick sections from FFPE	***For all patients:*** Baseline (Within 60 days of registration)
	Mandatory	FFPE blocks (preferred) or 2 unstained glass slides with 4-micron-thick sections from FFPE	***For patients who cross over from Group 1 to Group 2 only:*** At the time of disease progression

	Optional	FFPE blocks (preferred) or 2 unstained glass slides with 4-micron-thick sections from FFPE	***For all patients:*** At the time of disease progression

1. Kits will be provided by Mayo Clinic. To request kits, refer to Appendix E.

9.2 Integrated Correlative Studies

9.2.1 Quantification/Characterization of CD27+ cells in the Tumor Microenvironment by Immunohistochemistry (IHC)

9.2.1.1 Collection of Specimen(s): FFPE tumor tissue

9.2.1.2 Handling and Shipping of Specimen(s): FFPE tumor blocks are preferred. Alternatively, a minimum of 13 unstained glass slides with 4-micron thick sections from FFPE per collection timepoint are acceptable. Please include a copy of the de-identified surgical pathology report, as well as study, site and patient study numbers. All FFPE specimens for correlative studies may be shipped together.

Shipping Procedure:

1. Place the block or slides in small zip-lock bag and seal.
2. Insert the bag containing the block or the slides in a bubble wrap bag.
3. Place wrapped samples inside the largest compartment of specimen biohazard bag and seal.
4. Insert a copy of the de-identified surgical pathology report in the outer pocket of the specimen biohazard bag.
5. Include a refrigerated cold pack (not frozen) if shipping in the summer months.
6. Place the specimen biohazard bag into the box and close.
7. Complete the transport documents and place into waybill pouch; affix to box.
8. Ship package to Mayo Clinic at the address below.
9. Please send email on the day of the shipment.

Please send FFPE tissue to:

Predolin Biobank
Attn: Kim Henderson
Mayo Clinic
613 Stabile Building
221 4th Avenue SW
Rochester, MN 55905

9.2.1.3 Methodology: The integrated biomarker (CD27 IHC) assay will be performed on formalin-fixed paraffin-embedded (FFPE) tissue. Biopsies should be obtained under radiologic or other guidance, as appropriate, per institutional procedures. Tissues should be placed in preservative no later than 30 minutes following removal from the body (ideally with 5-10 minutes). If tissue is obtained via core biopsy, a minimum of 3 and up to 6 cores are requested; however, less than the goal amount of tissue is acceptable, and should be based upon the clinical judgment of the clinician performing the procedure. Based upon prior studies, it is feasible for up to 6 to 8 core biopsies to be obtained depending on the site being sampled, the size of the mass, and the safety of the procedure. Specimens should then be fixed using 10% Neutral Buffered formalin for 20 +/- 4 hours and then processed into FFPEs. If fixed specimens cannot be processed into FFPE within the period specified above, transfer the specimen to a container of 70% histology-grade alcohol where the specimen can be stable for up to 2 weeks. If the site cannot process tissue into FFPE, then ship specimens in 70% alcohol. Tissue blocks should be ideally released for the biomarker study. In the event this is not possible, serial 4 μm sections should be obtained from each core and mounted on positively-charged unstained glass slides. A total of 3 slides created from biopsy obtained at the time of registration should be forwarded from the Predolin Biobank to Mosaic Laboratories. A repeat biopsy is mandatory for patients who wish to cross-over from Group 1 to Group 2 in the event of progression. Three additional slides obtained at the time of progression should be forwarded from the Predolin Biobank to Mosaic Laboratories for these patients. Additional glass slides will be created for exploratory correlative studies as specified on section 9.1 (Specimen Requirements for Correlative Studies).

9.2.1.4 Statistical Analysis: We will use the “marker-by-treatment predictiveness curves” in Janes et al. to explore CD27 as a potential predictive biomarker for the benefit of Varlilumab. Specifically, we will display the response rate as a function of the percentiles of CD27 for each treatment arm: Varlilumab plus Nivolumab and Nivolumab alone. We will use logistic regression to model the response rate as a function of treatment and CD27 (as a continuous variable). The distribution of CD27 will be estimated empirically in the entire trial population and used to calculate CD27 values corresponding to each fixed percentile. If the two predictiveness curves cross (suggesting predictive potential of CD27), the point where the two curves cross would be a possible choice of threshold for dichotomizing CD27 into “low” versus “high”. Threshold levels shown to be best predictors of clinical outcomes will be considered as reference for later pivotal trials.

9.3 Exploratory/Ancillary Correlative Studies

9.3.1 Comprehensive Analysis of Peripheral Blood Immune Cells by Mass Cytometry (CyTOF)

9.3.1.1 Collection of Specimen(s): 12 mL peripheral blood collected in yellow top tubes (ACD).

9.3.1.2 Handling and Shipping of Specimens(s): Kits will be provided for the collection of blood samples. The kit contains supplies and instructions for collecting, processing, and shipping specimens. Refer to Appendix E for kit ordering, sample collection, and sample shipping instructions.

9.3.1.3 Methodology: CyTOF (cytometry at time-of-flight) or mass cytometry is a new platform that uses mass spectrometry to allow evaluation of at over 35 simultaneous parameters on a single-cell level. This technology uses nonradioactive non-biological metal isotopes as reporters tagged to monoclonal antibodies. Measurements are made based on mass spectrometry, which largely avoids the hurdles of interference and spectral overlap experienced with fluorochrome-based flow cytometry. This constitutes an ideal platform for the study of the tumor microenvironment or immune monitoring given its ability to assess a large number of parameters and resolve small differences in a heterogeneous population of cells.

Mononuclear cells will be isolated from patient's peripheral blood via gradient separation using a Ficoll sodium diatrizoate solution (Ficoll-Paque^{TM} PLUS, GE Healthcare). The resulting mononuclear single-cell suspension will be suspended in freezing media containing 10% dimethyl sulfoxide and stored in liquid nitrogen or -150^{o}C freezer for analysis. Specimens will be stained in batches of 3-4 patients. Unstimulated live single-cell suspensions will be stained with a cocktail of metal-tagged antibodies designed to recognize 34 surface proteins (Appendix F). Nucleated cellular events will be identified using a DNA intercalator conjugated to natural abundance iridium (^{191}Ir and ^{193}Ir). Cisplatin (^{195}Pt) will be used for dead-live cell discrimination and calibration beads containing natural abundance cerium ($^{140/142}$Ce), europium ($^{151/153}$Eu), holmium (^{165}Ho), and lutetium ($^{175/176}$Lu) will be used for normalization of acquired data. Our panel will be constructed using commercially available metal-conjugated antibodies (Fluidigm Corporation) and stained cells will acquired on the CyTOF2 (Fluidigm Corporation).

We will stain a minimum of 3 x 10^6 cells per specimen and acquire a minimum of 1 x 10^6 events on the CyTOF. We will initially perform high-level manual gating to exclude dead or apoptotic cells, debris, beads and doublets. Additional multiparametric analysis will be done using platforms such as Spanning-tree Progression Analysis of Density-normalized Events (SPADE) and visualization of unbiased clustering of events using the t-SNE (t-Distributed Stochastic Neighbor Embedding) algorithm or viSNE.

9.3.2 Identification/Characterization of Intratumoral Immune Cells by Immunohistochemistry (IHC) and CyTOF

9.3.2.1 Collection of Specimen(s): FFPE tumor tissue

9.3.2.2 Handling and Shipping of Specimens(s): FFPE tumor block(s) are preferred. Alternatively, a minimum of 13 unstained glass slides with 4-micron thick sections from FFPE per collection timepoint are acceptable. Please include a copy of the de-identified surgical pathology report, as well as study, site and patient study numbers. All FFPE specimens for correlative studies may be shipped together.

Shipping Procedure:

1. Place the block or slides in small zip-lock bag and seal.
2. Insert the bag containing the block or the slides in a bubble wrap bag.
3. Place wrapped samples inside the largest compartment of specimen biohazard bag and seal.
4. Insert a copy of the de-identified surgical pathology report in the outer pocket of the specimen biohazard bag.
5. Include a refrigerated cold pack (not frozen) if shipping in the summer months.
6. Place the specimen biohazard bag into the box and close.
7. Complete the transport documents and place into waybill pouch; affix to box.
8. Ship package to Mayo Clinic at the address below.
9. Please send email on the day of the shipment.

Please send FFPE tissue to:

Predolin Biobank
Attn: Kim Henderson
Mayo Clinic
613 Stabile Building
221 4th Avenue SW
Rochester, MN 55905

9.3.2.3 Methodology: Serial 4-µm paraffin-embedded sections will be used for IHC. The tissue will be deparaffinized with three changes of xylene and cleared through graded series of ethanol. Endogenous peroxidase will be quenched by incubation in 50% methanol/H2O2 and after rinsing with tap water; all sections will be pretreated for 30 minutes with 50 mmol/L EDTA using a steamer and cooled for additional 5 minutes. All staining will be done automatically on DAKO Autostainer using the following antibodies to CD11c (Leica Microsystems 5D11), CD14 (Cell Marque EPR 3653), CD163 (DAKO 1F8), CD68 (DAKO PG-M1), CXCL13 (R&D Systems 53610), FOXP3 (Abcam 236AE/7), CD3 (R&D Systems), PD-L1 (405.9A11), PD-L2 (366C.9E5), CD8a (Dako M7103) and PD-1 (Abcam NAT). The sections will be viewed with an Olympus BXFA51 microscope and pictures taken with an Olympus DP71 camera. Stained slides will be scored by expert hematopathologist. Internal control (reactive lymph node, tonsil) will be used to verify staining quality. Analysis of intra-tumoral immune cell subsets by IHC will be largely exploratory and reported descriptively.

For CyTOF analysis of intra-tumoral immune cells, we will perform multiparametric staining of single-cell suspensions obtained from FFPE blocks using the FFPE-

DISSECT (disaggregation for intracellular signaling in single epithelial cells from tissue) method. Single cells will be stained with the same 34-parameter surface protein panel (Appendix F). Nucleated cellular events will be identified using a DNA intercalator conjugated to natural abundance iridium (^{191}Ir and ^{193}Ir). Cisplatin (^{195}Pt) will be used for dead-live cell discrimination and calibration beads containing natural abundance cerium ($^{140/142}$Ce), europium ($^{151/153}$Eu), holmium (^{165}Ho), and lutetium ($^{175/176}$Lu) will be used for normalization of acquired data. Our panel will be constructed using commercially available metal-conjugated antibodies (Fluidigm Corporation) and stained cells will acquired on the CyTOF2 (Fluidigm Corporation).

We will stain a minimum of 3 x 10^6 cells per specimen and acquire a minimum of 1 x 10^6 events on the CyTOF. We will initially perform high-level manual gating to exclude dead or apoptotic cells, debris, beads and doublets. Additional multiparametric analysis will be done using platforms such as Spanning-tree Progression Analysis of Density-normalized Events (SPADE) and visualization of unbiased clustering of events using the t-SNE (t-Distributed Stochastic Neighbor Embedding) algorithm or viSNE.

9.3.3 Evaluation of Genetic Alterations in Chromosome 9p24.1 by FISH

9.3.3.1 Collection of Specimen(s): FFPE tumor tissue

9.3.3.2 Handling and Shipping of Specimens(s): FFPE tumor blocks are preferred. Alternatively, a minimum of 13 unstained glass slides with 4-micron thick sections from FFPE per collection timepoint are acceptable. Please include a copy of the de-identified surgical pathology report, as well as study, site and patient study numbers. All FFPE tissue for correlative studies may be shipped together.

Shipping Procedure:

1. Place the block or slides in small zip-lock bag and seal.
2. Insert the bag containing the block or the slides in a bubble wrap bag.
3. Place wrapped samples inside the largest compartment of specimen biohazard bag and seal.
4. Insert a copy of the de-identified surgical pathology report in the outer pocket of the specimen biohazard bag.
5. Include a refrigerated cold pack (not frozen) if shipping in the summer months.
6. Place the specimen biohazard bag into the box and close.
7. Complete the transport documents and place into waybill pouch; affix to box.
8. Ship package to Mayo Clinic at the address below.
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Attn: Kim Henderson

Mayo Clinic
613 Stabile Building
221 4th Avenue SW
Rochester, MN 55905

9.3.3.3 Methodology: The bacterial artificial chromosome probes (CHORI; www.chori.org) RP11-599H2O, which maps to 9p24.1 and includes CD274 (encoding PD-L1, labeled with Spectrum Orange), and RP11-635N21, which also maps to 9p24.1 and includes PDCD1LG2 (encoding PD-L2, labeled with Spectrum Green), will be cohybridized. A control centromeric probe, Spectrum Aqua–labeled CEP9 (Abbott Molecular) that maps to 9p11-q11, will be hybridized according to the manufacturer's recommendations. Nuclei with a target:control probe ratio of at least 3:1 will be classified as amplified, those with a probe ratio of more than 1:1 but less than 3:1 will be classified as relative copy gain, and those with a probe ratio of 1:1 but with more than two copies of each probe will be classified as polysomic for chromosome 9p. Analysis of genetic alterations Involving chromosome 9p24.1 by FISH will be largely exploratory and reported descriptively.

9.3.4 Evaluation of Serum Cytokine Profile by ELISA

9.3.4.1 Collection of Specimen(s): 10 mL of peripheral blood collected in red top tubes (No anticoagulant)

9.3.4.2 Handling and Shipping of Specimens(s): Kits will be provided for the collection of blood samples. The kit contains supplies and instructions for collecting, processing, and shipping specimens. Refer to Appendix E for kit ordering, sample collection, and sample shipping instructions.

9.3.4.3 Methodology: Serial serum samples will be collected every 14 days before infusion of study drugs for the first 12 weeks of the study. Samples will be subjected to multiplex ELISA (Invitrogen, Camarillo, CA) to measure 30 serum cytokines. Luminex-200 system version 1.7 will be used for reading plates and MasterPlex QT1.0 system (MiraiBio) will be used to analyze data. Cytokines will include epidermal growth factor (EGF), eotaxin, basic fibroblast growth factor (FGF-b), granulocyte macrophage colony stimulating factor (GM-CSF), hepatocyte growth factor (HGF), IFN-α, IFN-ϒ, interleukin 1 receptor antagonist (IL-1RA), IL-1β,IL-2, IL-2R , IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17, IP10, MCP-1, MIG, MIP-1α (CCL3), MIP1β (CCL4), regulated on activation normal T-cell expressed and secreted (RANTES), TNF-α and vascular endothelial growth factor (VEGF). Internal control serum will be included in all assays to control for inter-assay variation. Analysis of the serum cytokine by multiplex ELISA will be largely exploratory and reported descriptively.

9.3.5 Evaluation of Pharmacokinetics and Immunogenicity of CDX-1127 (varlilumab) and Nivolumab

9.3.5.1 Collection of Specimen(s): 20 mL of peripheral blood collected in red top tubes (No anticoagulant)

9.3.5.2 Handling and Shipping of Specimens(s): Kits will be provided for the collection of blood samples. The kit contains supplies and instructions for collecting, processing, and shipping specimens. Refer to Appendix E for kit ordering, sample collection, and sample shipping instructions.

9.3.5.3 Methodology: The pharmacokinetic properties and the ability of the study drugs to elicit an immunogenic response will be evaluated using standardized assays performed at their respective companies for the two study drugs. Blood draws will be obtained at baseline, pre-dose prior to the administration of drugs for the first 4 cycles, at end of treatment, and at the time of safety follow-up (if available) for all patients. Patients randomized to Group 1 who cross-over to Group 2 will need 4 additional blood draws to evaluate for immunogenicity to CDX-1127 (varlilumab) obtained pre-dose prior to the administration of the 4 initial doses of that medication.

9.3.6 Evaluation of Mutational Burden as a Biomarker for Response to Checkpoint Blockade Therapy

9.3.6.1 Collection of Specimen(s): FFPE tumor tissue

9.3.6.2 Handling and Shipping of Specimens(s): FFPE tumor blocks are preferred. Alternatively, a minimum of 13 unstained glass slides with 4-micron thick sections from FFPE per collection timepoint are acceptable. Please include a copy of the de-identified surgical pathology report, as well as study, site and patient study numbers. All FFPE tissue for correlative studies may be shipped together.

Shipping Procedure:

1. Place the block or slides in small zip-lock bag and seal.
2. Insert the bag containing the block or the slides in a bubble wrap bag.
3. Place wrapped samples inside the largest compartment of specimen biohazard bag and seal.
4. Insert a copy of the de-identified surgical pathology report in the outer pocket of the specimen biohazard bag.
5. Include a refrigerated cold pack (not frozen) if shipping in the summer months.
6. Place the specimen biohazard bag into the box and close.
7. Complete the transport documents and place into waybill pouch; affix to box.
8. Ship package to Mayo Clinic at the address below.

9. Please send email on the day of the shipment.

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Attn: Kim Henderson
Mayo Clinic
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221 4th Avenue SW
Rochester, MN 55905

9.3.6.3 Methodology: Genomic DNA will be extracted from formalin-fixed, paraffin-embedded (FFPE) tissue blocks or slides. Hematoxylin and eosin (H&E) stained sections from each case will be reviewed by an expert hematopathologist and representative blocks with at least 30% tumor cells will be selected. Sections of 10 x 4-micron dimensions will be cut from blocks (based on tissue area of 25 mm^2). DNA will be extracted using the Qiagen FFPE DNA extraction kit. DNA quantitation will be performed using a Qubit fluorometer prior to sequencing. Whole exome analysis of paired tumor and normal tissue will be performed using Ion TorrentTM platform at the Molecular Characterization and Clinical Assay Development Laboratory, Leidos Biomedical Research Inc., Frederick National Laboratory for Cancer Research. The analysis of mutational burden by whole exome sequencing is largely exploratory and reported descriptively

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to registration unless stated otherwise. Biopsy for FFPE may be obtained within 60 days prior to registration. Scans and x-rays must be done ≤ 4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. The frequency of routine evaluations (physical, vital signs, routine laboratory tests) changes from every 2 weeks to every 4 weeks after 4 months to accommodate the change in administration schedule of nivolumab.

		Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycles 5 and beyond*	
	Pre-Study	Week 1	Week 3	Week 5	Week 7	Week 9	Week 11	Week 13	Week 15	Week 17 and beyond	Off Study[d]
CDX-1127 (Varlilumab)		V		V		V		V		V	
Nivolumab		N	N	N	N	N	N	N	N	N	
Informed consent	X										
Demographics	X										
Medical history	X										
Concurrent meds	X	X	X	X	X	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Height	X										
Weight	X	X	X	X	X	X	X	X	X	X	X
Oxygen saturation	X	X	X	X	X	X	X	X	X	X	X
Performance	X	X	X	X	X	X	X	X	X	X	X

status											
Lab tests [a]	X	X	X	X	X	X	X	X	X	X	X
Evaluation of Cardiac Function [e]	X										
Adverse event evaluation		X	X	X	X	X	X	X	X	X	X
Radiologic evaluation	X		Radiologic measurements should be performed every 12 weeks from C1D1 (+/- 3 days). Documentation (radiologic) should must be provided for patients removed from study for progressive disease								
B-HCG	X[b]	X[g]									
FFPE for correlatives	X[c]										X[c]
Blood for correlatives[f]	X	X	X	X	X	X	X				

V: CDX-1127 (Varlilumab): ***Group 2 Patients only***: 3 mg/kg every 4 weeks ± 2 days

N: Nivolumab: ***All patients:*** 240 mg every 2 weeks ± 2 days for 4 months followed by 480 mg every 4 weeks thereafter

a: Lab tests to be performed at baseline and within 72 hours prior to each study drug administration include complete blood count (CBC) with differential; albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN/urea, calcium, magnesium, chloride, creatinine, fasting glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, amylase, lipase, TSH (with reflexive Free T4 and Free T3). Laboratory test monitoring will continue as long as patient continues to receive study treatment.

b: Serum or urine pregnancy test for females of childbearing potential.

	c. A pre-study biopsy is mandatory for all groups and must be obtained within 60 days prior to registration. For Group 1 patients who elect to cross over to Group 2, a biopsy is mandatory at that time. An off-study biopsy is optional for all groups. d: Off-study evaluation to be performed 30 days (+/- 14 days) after the last dose of study drug. Patients are followed for at least 100 days for AE assessment. e: As clinically indicated, perform an evaluation of cardiac function including ECG and echocardiogram for any patients with a history of CHF or at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs. Also perform an evaluation for patients with evidence of CHF, MI, cardiomyopathy, or myositis including lab tests and cardiology consultations including ECG, echocardiogram, CPK and troponin. f: Blood draw for correlative studies will be obtained at baseline (within 14 days prior to start of protocol therapy) and within 72 hours prior to the administration of any of the study drugs on dosing days. These blood draws may be performed at the same occasion as other laboratory tests obtained for the purpose of clinical monitoring of the patient. Patients who cross-over from Group 1 to Group 2 will need 4 additional blood draws pre-dose prior to their first 4 infusions of CDX-1127 (varlilumab) for immunogenicity and PK studies. g: A serum or urine pregnancy test is required within 24 hours of starting study treatment. If the pre-study assessment was performed within 24 hours prior to start of study treatment, a pregnancy test does not need to be repeated. *: Starting with Cycle 5 (Week 17), the dosage and administration schedule of nivolumab is changed to 480 mg every 4 weeks. The dosage and administration schedule of CDX-1127 (varlilumab) remains unchanged. Once the schedule of administration of nivolumab changes, the frequency of routine evaluations also changes accordingly to every 4 weeks as well.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Hematological Tumors

11.1.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with CDX-1127 (varlilumab) and/or nivolumab

Evaluable for objective response: All patients fulfilling eligibility criteria that have signed a consent form and have begun treatment will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

11.1.2 Response Criteria

Patients will be evaluated for efficacy based on the lymphoma response to immunomodulatory therapy criteria or LYRIC (Cheson *et al.,* 2016).

11.1.3 Schedule of Evaluations

PET/CT scans are required at baseline for all patients. Repeat PET-CT scans should be obtained every 12 weeks unless otherwise clinically indicated.

Definitions for clinical response for patients with lymphoma are based on the lymphoma response to immunomodulatory therapy criteria or LYRIC (Cheson *et al.,* 2016). Lymph node measurements should be taken from the CT portion of the PET/CT, or other dedicated CT scans where applicable. Measurement of lymphadenopathy for purposes of assessing for PR will be determined by adding the sum of the products of the maximal perpendicular diameters of measured lesions (SPD). The perpendicular diameter of a single node is sufficient to evaluate for PD (see Table 11.1.4). Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (*e.g.*, pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically and pathologically negative.

For response assessment, PET-CT is preferred for staging of FDG-avid lymphomas and CT scan is preferred in the other lymphomas

Progressive disease is based on either PET-CT based (PMD) or CT based (PD) response criteria. Definition of progressive disease according to LYRIC is same as the Lugano classification except that a new category of indeterminate response (IR) is added. Patients whose disease fall in the IR category may continue treatment for additional 12 weeks if the patient remains clinically stable as judged by the treating physician. A repeat imaging

study in 12 weeks (or earlier if clinically indicated) is mandatory to confirm or refute disease progression. PET confirmation of progressive disease is per physician discretion.

11.1.4 Lymphoma Response to Immunomodulatory Therapy Criteria [LYRIC] (adapted from Cheson *et al.,* 2016)

	PET-CT Based Response	**CT-Based Response**
Complete Response (CR)	**Complete metabolic response (CMR)**	**Complete radiologic response (CR) (all of the following)**
Lymph nodes and extra lymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (*e.g.,* with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extra lymphatic sites of disease
Non-measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial Response (PR)	**Partial metabolic response (PMR)**	**Partial remission (PR) (all of the following)**
Lymph nodes and extra lymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm X 5 mm as the default value When no longer visible, 0 X 0 mm For a node > 5 mm X 5 mm, but

	PET-CT Based Response	CT-Based Response
		smaller than normal, use actual measurement for calculation
Non-measured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not Applicable
No Response or Stable Disease	**No metabolic response (NMR)**	**Stable disease (SD)**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Non-measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not Applicable
Indeterminate Response (IR)		
IR(1)[b]		≥ 50% increase in SPD of up to 6 measurable lesions in first 12 weeks without clinical deterioration. **Note:** The measurements from the first IR (1) time point becomes the reference against which future assessment will be compared. An increase of ≥ 10% (in addition to an increase of ≥ 5 mm in either dimension of ≥ 1 lesion for lesions ≤

	PET-CT Based Response	CT-Based Response
		2cm and 10 mm for lesions > 2 cm) constitutes PD
IR(2)		< 50% increase in SPD of up to 6 measurable lesions with: a. new lesion(s), or b. ≥ 50% increase in PPD of a lesion or set of lesions at any time during treatment. **Note:** The new or growing lesion(s) (unless biopsy proven to be benign) should be added to the target lesion(s), up to a total of no more than 6 total lesions. In future assessments, if the SPD of the newly defined set of target lesions has increased ≥ 50% from their nadir value (which may precede the IR time point), the patient should be considered to have PD.
IR(3)	Increase in FDG uptake of 1 or more lesion(s) without a concomitant increase in lesion size or number. **Note:** Because inflammatory responses may result in an increase in the standardized uptake value of a lesion, the patient will not be considered to have PD unless there is evidence of PD by an increase in lesion size or the development of new lesions, as noted below.	
Progressive disease (PD)	***** Excludes patients who meet criteria for Indeterminate Response (IR) *****	
	Progressive metabolic disease (PMD)	**Progressive disease (PD) requires at least 1 of the following**
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >
Extranodal lesions		

	PET-CT Based Response	CT-Based Response
		50% of the extent of its prior increase beyond baseline (*e.g.*, a 15 cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Non-measured lesions	None	New or clear progression of preexisting non-measured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (*e.g.*, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

a. A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid under treatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (*e.g.*, liver, spleen, kidneys, and lungs), GI involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (*e.g.*,, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (*e.g.*, with marrow activation as a result of chemotherapy

	PET-CT Based Response	CT-Based Response
or myeloid growth factors). † PET Deauville 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma. b. If a patient is assessed as having IR and then "true" PD at a subsequent time point (without an intervening objective response between IR and PD), the IR assessment should subsequently be corrected to PD for reporting purposes to the date of the prior designation of IR. We recognize that these lesions may remain stable during the time of observation, but, even if this is the case, the initial designation of IR should be changed to PD.		

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Study Oversight

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

During the initial phase of the study (before the interim futility analysis), the Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators to review accrual, progress, and pharmacovigilance. Decisions to proceed with the study beyond the interim analysis will require sign-off by the Protocol Principal Investigator and the Protocol Statistician.

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

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

12.2 Data Reporting

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

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

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

12.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

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

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

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

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

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

12.3 CTEP Multicenter Guidelines

Not Applicable.

12.4 Collaborative Agreements Language

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

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

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

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

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

    c. Any Collaborator having the right to use the Multi-Party Data from these

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

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

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

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

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

Email: ncicteppubs@mail.nih.gov

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

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

13.1.1 Overview

This is a phase 2 study designed to evaluate the safety and efficacy of the addition of nivolumab to CDX-1127 (varlilumab) for patients with advanced high-grade B-cell NHL. The study will utilize a randomized phase 2 study design to determine the anti-tumor activity of combination therapy with CDX-1127 (varlilumab) and nivolumab (Group 2; experimental group) as compared to nivolumab alone (Group 1; control group), where response will be evaluated based on the LYRIC response criteria.

13.1.2 Primary Endpoint

The primary endpoint of this trial is the overall response rate, which will be compared between the two groups. A response will be defined as an objective status of PR or CR for patients evaluated by CT-based criteria and CMR or PMR for patients evaluated by PET-CT based criteria. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for overall response.

13.1.3 Statistical Design

Decision Rule: A randomized trial comparing combination therapy with CDX-1127 (varlilumab) and nivolumab as compared to nivolumab alone will be conducted as described by Rubinstein. We will enter 48 evaluable patients on each group of the study using a 1:1 randomization scheme where patients are stratified based on age (< 65 vs. ≥ 65 years), previous autologous stem cell transplant (yes vs. no), and diagnosis category per Section 3.1.1 (A vs. B). Randomization will be done using a (stratified) permuted block design with randomly varying block sizes. A sample size of 48 patients per group provides 80% power to detect an improvement in response rate from 25% to 45%, using a one-sided test at a significance level of 0.15 (nQuery 7.0).

This estimated response rate is based on the clinical efficacy demonstrated by Nivolumab in the phase II trial (Lesokhin et al, JCO 2016). In that study 11 patients with DLBCL were treated with Nivolumab, of which 4 (36%) achieved an objective response. Nonetheless, at the time of publication only 1 of those maintained a response while 2 were still being followed (3 of 11 or 27%). Unpublished data from a larger phase 2 trial appears to have a low response rate for nivolumab alone with an overall response rate that appears to be $< 20\%$. We therefore selected 25% as our best estimate of response for nivolumab alone.

Interim Analysis Decision Rule: An interim analysis with a futility rule will be performed after half of the patients (24 patients in each group) have completed their first radiologic scan after 3 cycles (12 weeks of treatment or up to 20 weeks if treatment delays occurred). At the time of the interim analysis, we will compare the response rate of Group 2 the experimental group to Group 1 the control group. If the

response rate in Group 2 the experimental group is less than the response rate in Group 1 the control group, we will consider this early evidence that the Group 2 the experimental group does not have a higher overall response rate and accrual will be terminated. Otherwise, we will continue accrual (Wieand *et al*., 1994)

Final Decision Rule: The final analysis will take place after all 48 evaluable patients in each group have been followed for at least 6 months. The response rates will be compared between the two groups using Fisher's exact test. If the response rate is higher in Group 2 the experimental group, where the p-value < 0.15, this will be considered sufficient evidence that Group 2 the experimental group may be recommended for further testing in subsequent studies. Otherwise, we will conclude that there is not statistical evidence of superiority of the experimental regimen.

Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process however, they will be included in final point estimates and confidence intervals.

NOTE: The trial will not be halted while the first 24 patients in each group are evaluated for the interim analysis. However, if the accrual is especially rapid, we may temporarily suspend accrual to prevent missing important acute toxicity patterns.

Other Considerations: Toxicity, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

13.1.4 Analysis Plan

The analysis for this trial will commence at planned time points and at the time the patients have become evaluable for the primary endpoint. Such a decision will be made by the Statistician and Study Chair, in accord with ETCTN Standard Operating Procedures, availability of data for secondary endpoints (eg, laboratory correlates), and the level of data maturity. It is anticipated that the earliest date in which the results will be made available via manuscript, abstract, or presentation format is when the last patient has been followed for at least 6 months.

13.1.5 Primary Endpoint

Definition: The primary endpoint of this trial is the overall response rate, which will be compared between the two arms. A response will be defined as an objective status of PR or CR for patients evaluated by CT-based criteria and CMR or PMR for patients evaluated by PET-CT based criteria. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for overall response.

Estimation: The proportion of successes will be estimated in each arm by the number of successes divided by the total number of evaluable patients. Exact binomial ninety-five percent confidence intervals for the true success proportion will be calculated in

each arm. Comparison of overall response rates between the two treatment groups will be performed using a one-sided Fisher's exact test at significance level 0.15.

13.2 Sample Size/Accrual Rate

13.2.1 Sample Size

A maximum of 96 evaluable patients (48 in each group) will be accrued unless undue toxicity is encountered. We anticipate accruing an additional 10 patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Maximum projected accrual is 106 patients.

13.2.2 Accrual Rate and Study Duration

The anticipated accrual rate is approximately 5-6 patients per month. Therefore, the accrual period for this phase 2 study is expected to be about 20 months. The final analysis can begin approximately 26 months after the trial begins, i.e. as soon as the final patient accrued to this trial has been followed for at least 6 months.

13.2.3 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender or ethnic origin.

There is no information currently available regarding differential effects of this regimen in subsets defined by race or gender, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

Based on prior studies involving similar disease sites, we expect about 30-35% of patients will be classified as minorities by race and about 40% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

PLANNED ENROLLMENT REPORT

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	1	0	0	**1**
Asian	2	3	0	0	**5**
Native Hawaiian or Other Pacific Islander	0	1	0	0	**1**

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
Black or African American	5	8	0	0	**13**
White	30	44	4	5	**83**
More Than One Race	1	1	0	1	**3**
Total	**38**	**58**	**4**	**6**	**106**

13.3 Stratification Factors

13.3.1 Age group: < 65 years or ≥ 65 years

13.3.2 Previous autologous stem cell transplant: yes vs. no

13.3.3 Diagnosis category (per section 3.1.1): Category A vs. Category B

13.4 Analysis of Secondary Endpoints

13.4.1 Duration of Response

Duration of response is defined for all evaluable patients who have achieved a response as the date at which the patient's objective status is first noted to be a PR or CR for patients evaluated by CT-based criteria or CMR or PMR for patients evaluated by PET-CT based criteria to the earliest date progression (PMD or PD) is documented. If a patient has not had disease progression, they will be censored on the date of their last disease assessment. The distribution of duration of response will be estimated using the method of Kaplan-Meier. The comparison of duration of response between two treatment arms will be based on the log-rank test.

13.4.2 Survival Time

Survival time is defined as the time from randomization to death due to any cause. The distribution of survival time will be estimated using the method of Kaplan-Meier. The comparison of overall survival between two treatment arms will be based on the log-rank test.

13.4.3 Progression Free Survival

Progression free survival is defined as the time from randomization to the earliest

date of documentation of disease progression (PMD or PD) or death due to any cause. The distribution of progression-free survival will be estimated using the method of Kaplan-Meier. The comparison of progression-free survival between two treatment arms will be based on the log-rank test.

13.4.3.1 Adverse Events

All patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed for each arm to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration. The overall adverse event rates for Grade 3 or higher hematologic and non-hematologic adverse events at least possibly related to treatment will be compared between the two treatment groups using the Chi-square test (or Fisher's exact test if the data in the contingency table is sparse).

13.5 Analysis of Exploratory Endpoints

To determine the effect of combination therapy with CDX-1127 (varlilumab) and nivolumab on the immune system as assessed by immunohistochemistry (IHC), mass cytometry (CyTOF) and changes in serum cytokine profile, multiple measures will be evaluated. For each measure below, baseline values and changes in these parameters over time will be both graphically and quantitatively summarized and explored. Standard paired comparisons methodologies (Wilcoxon signed rank and McNemar's tests) will be used to assess changes in these variables before and after therapy. In addition, baseline values and changes over time in each measure will be explored in relation to clinical outcome. Differences between responders and non-responders will be assessed using Wilcoxon's rank sum (continuous data) or Fisher's exact (categorical data) test. The relationship between each measure and time to event measures (PFS, OS) will be evaluated using Cox's proportional hazards models and log-rank tests.

- CD27 IHC: CD27 expression will be evaluated in terms of level (an ordinal variable such as low, medium, high), % of cells expressing, and location (expression in tumor cells vs. expression in normal immune cells). The expression level can be gathered continuously and may also be evaluated as a categorical variable (low, medium, high expression for example). These values will be evaluated as predictors of response. This is the only integrated biomarker. The expression level of CD27 will be analyzed using the "marker-by-treatment predictiveness curves" in Janes et al. to explore CD27 as a potential predictive biomarker for the benefit of Varlilumab. Specifically, we will display the response rate as a function of the percentiles of CD27 for each treatment arm: Varlilumab plus Nivolumab and Nivolumab alone. We will use logistic regression to model the response rate as a function of treatment and CD27 (as a continuous variable). The distribution of CD27 will be estimated empirically in the entire trial population and used to calculate CD27 values corresponding to each fixed percentile. If the two predictiveness curves cross (suggesting predictive potential of CD27), the point where the two curves cross would be a possible choice of threshold for dichotomizing CD27 into "low" versus "high". Threshold levels

shown to be best predictors of clinical outcomes will be considered as reference for later pivotal trials.

- Analysis of Peripheral Blood Immune cells by Mass Cytometry (CyTOF): The patient's peripheral blood will be evaluated serially (at baseline and every 14 days for the first 12 weeks on study). The assay will detect and quantify the presence of specific subpopulations of immune cells (expressed as % of parent). In this exploratory analysis the relationship between presence/absence of a particular subtype of cell and association with outcomes will be evaluated. Evaluation of particular combinations of immune cells (immune signature) and whether they are predictive of outcome will also be evaluated.

- Identification/Characterization of Intratumoral Immune cells by IHC and CyTOF: Immune cell subpopulations in the neighborhood around the tumor will be evaluated with this assay. This is similar to above (CyTOF on peripheral blood) but in this case the assessment is made on the tumor biopsy specimen. The presence/absence of different subsets will be identified and quantified and the association with clinical outcomes will be evaluated as specified above. This is another exploratory biomarker.

- Evaluation of Genetic Alterations of Chromosome 9p24.1 by FISH: This chromosomal region will be evaluated and patients will be categorized in 4 groups: normal, amplified, relative copy gain or polysomy. The proportion of patients in each of these groups who achieve a response will be evaluated. This is another exploratory biomarker.

- Evaluation of Serum Cytokine Profile by ELISA: Serially collected peripheral blood (at baseline and every 14 days for the first 12 weeks on study) will be analyzed. The levels (continuous variable) of 30 different cytokines will be assessed at each of those time points. The elevation or decrease in any individual cytokine or a combination of them will be explored, as well as the association with outcomes. This is another exploratory biomarker.

- Evaluation of Mutation Burden by WES: Tumor tissue will undergo whole-exome sequencing to determine if the amount of mutations (continuous) is associated with outcome. This is another exploratory biomarker.

13.6 Reporting and Exclusions

13.6.1 Evaluable for Toxicity
All patients will be evaluable for toxicity from the time they start treatment.

13.6.2 Evaluation of Response
Ineligible patients who have signed a consent form, enrolled, and initiated treatment, will be considered evaluable for adverse events.

13.6.2.1 Ineligible

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment at the discretion of the physician as long as there are no safety concerns and the patient was properly registered. Sites should send a dated report and all relevant source documents to Mayo Clinic to the attention of the QAS at the address in Section 4.3.1.

Protocol stipulations, including follow-up, safety reporting, dose modification, off treatment criteria should be followed as for other patients on protocol.

13.6.2.2 Major Violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient may continue treatment at the discretion of the physician as long as there are no safety concerns and the patient was properly registered. Sites should send a dated report and all relevant source documents to Mayo Clinic to the attention of the QAS at the address in Section 4.3.1.

Protocol stipulations, including follow-up, safety reporting, dose modification, off treatment criteria should be followed as for other patients on protocol.

13.6.2.3 Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. Sites should send a dated report and all relevant source documents to Mayo Clinic to the attention of the QAS at the address in Section 4.3.1.

Data is to be submitted for all patients who cancel, including query resolution, for all data required to be submitted through the date the patient cancelled. No further follow-up is required.

13.7 Adverse Event Stopping Rule

The stopping rule applies to each group independently.

The stopping rule specified below is based on the knowledge available at study development. We note that the rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatments under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to both groups if at any time we observe events considered relevant to the study treatment (defined as any adverse events except those receiving the "unrelated" attribution) that satisfy one of the following in either of the groups (evaluated in each group separately):

- if 4 or more patients in the first 20 treated patients in the group experience a grade 4 or higher non-hematologic adverse event relevant to treatment.

- if after the first 20 patients have been treated, 20% of all patients in the group experience a grade 4 or higher non-hematologic adverse event relevant to treatment.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

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

APPENDIX B: PATIENT WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team

The patient _____ is enrolled on a clinical trial using the experimental study drugs, CDX-1127 (varlilumab) and nivolumab. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

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

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

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

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

Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD You are enrolled on a clinical trial using the experimental study drugs CDX-1127 (varlilumab) and nivolumab. This clinical trial is sponsored by the NCI. It is very important to: ➢ Tell your doctors if you stop taking any medicines or if you start taking any new medicines. ➢ Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	➢ Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements . ➢ Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____.

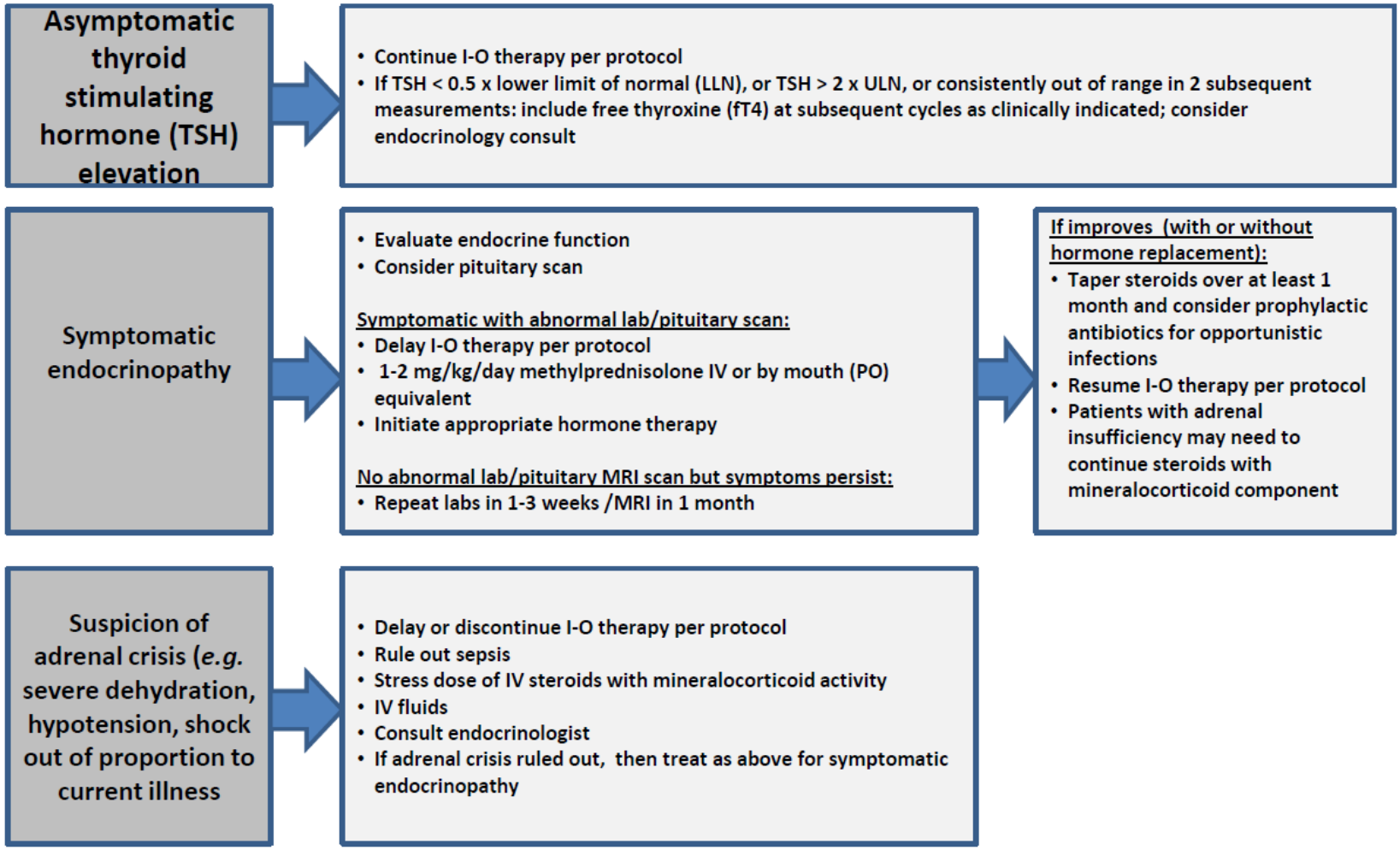
APPENDIX C: BIOASSAY TEMPLATES

The CD27 assay is commercially available from Mosaic Laboratories, LLC. CD27 expression and localization on tumor biopsies will be assessed by immunohistochemistry using analytically validated assay performed according to the vendor protocols and SOPs. This assay has been approved by the Biomarker Review Committee (BRC) of the Cancer Therapy Evaluation Program (CTEP)

APPENDIX D: MANAGEMENT ALGORITHMS FOR ENDOCRINOPATHY, GASTROINTESTINAL, HEPATIC, NEUROLOGICAL, PULMONARY, RENAL, AND SKIN ADVERSE EVENTS

Endocrinopathy Management Algorithm

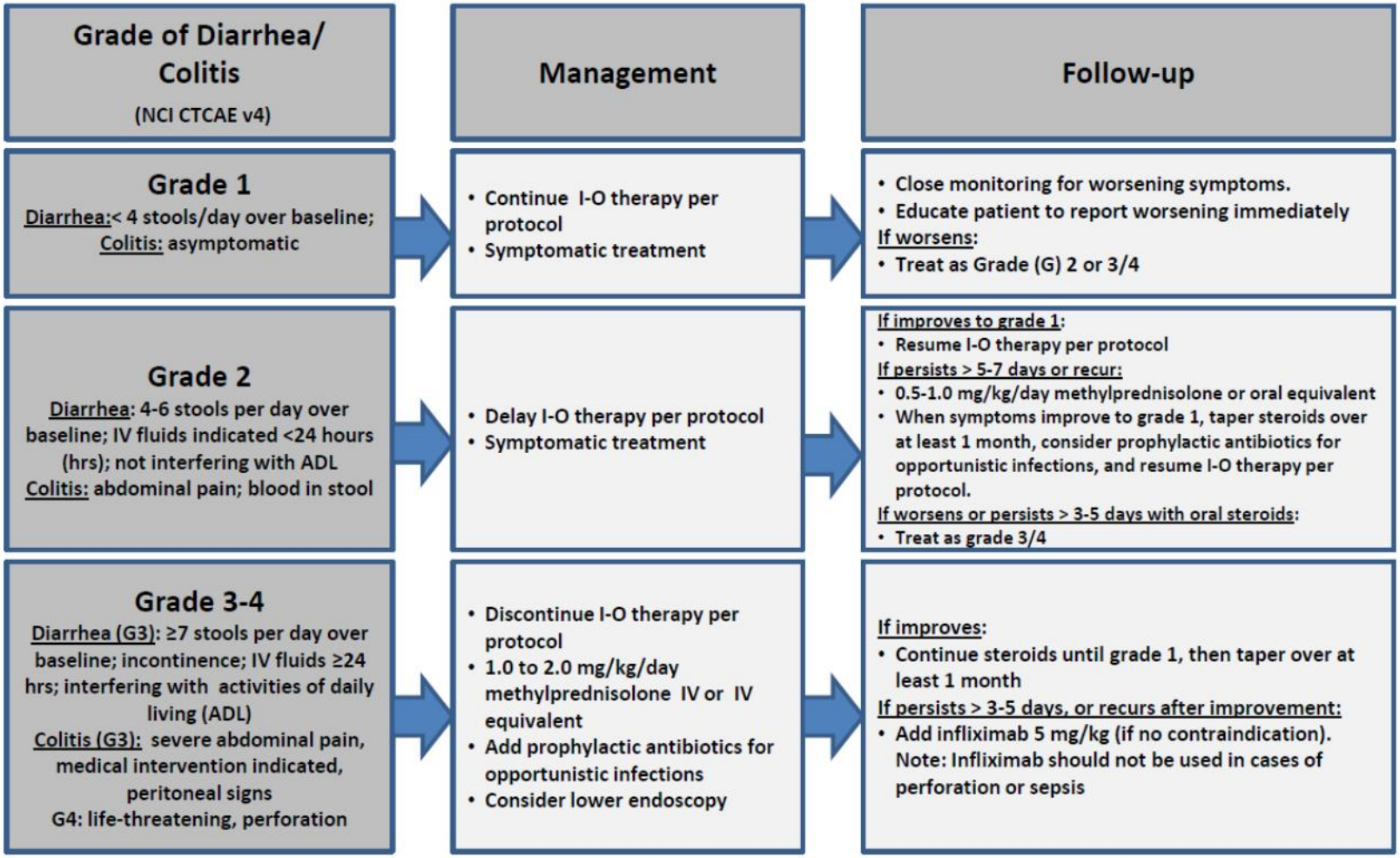
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue immuno-oncology (I-O) therapy.
Consider visual field testing, endocrinology consultation, and imaging.



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

GI Adverse Event Management Algorithm

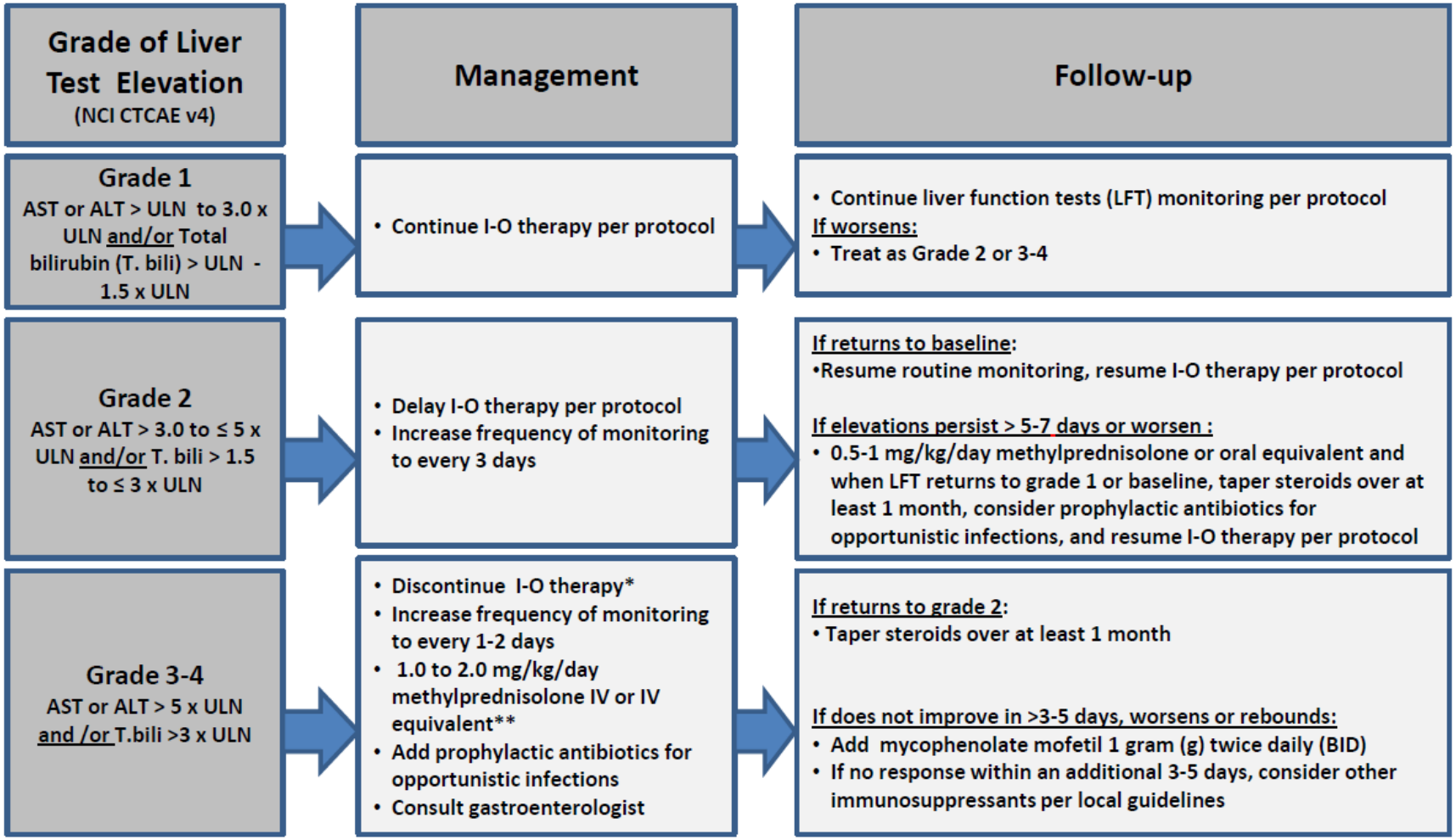
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

Hepatic Adverse Event Management Algorithm

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



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

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

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

Neurological Adverse Event Management Algorithm

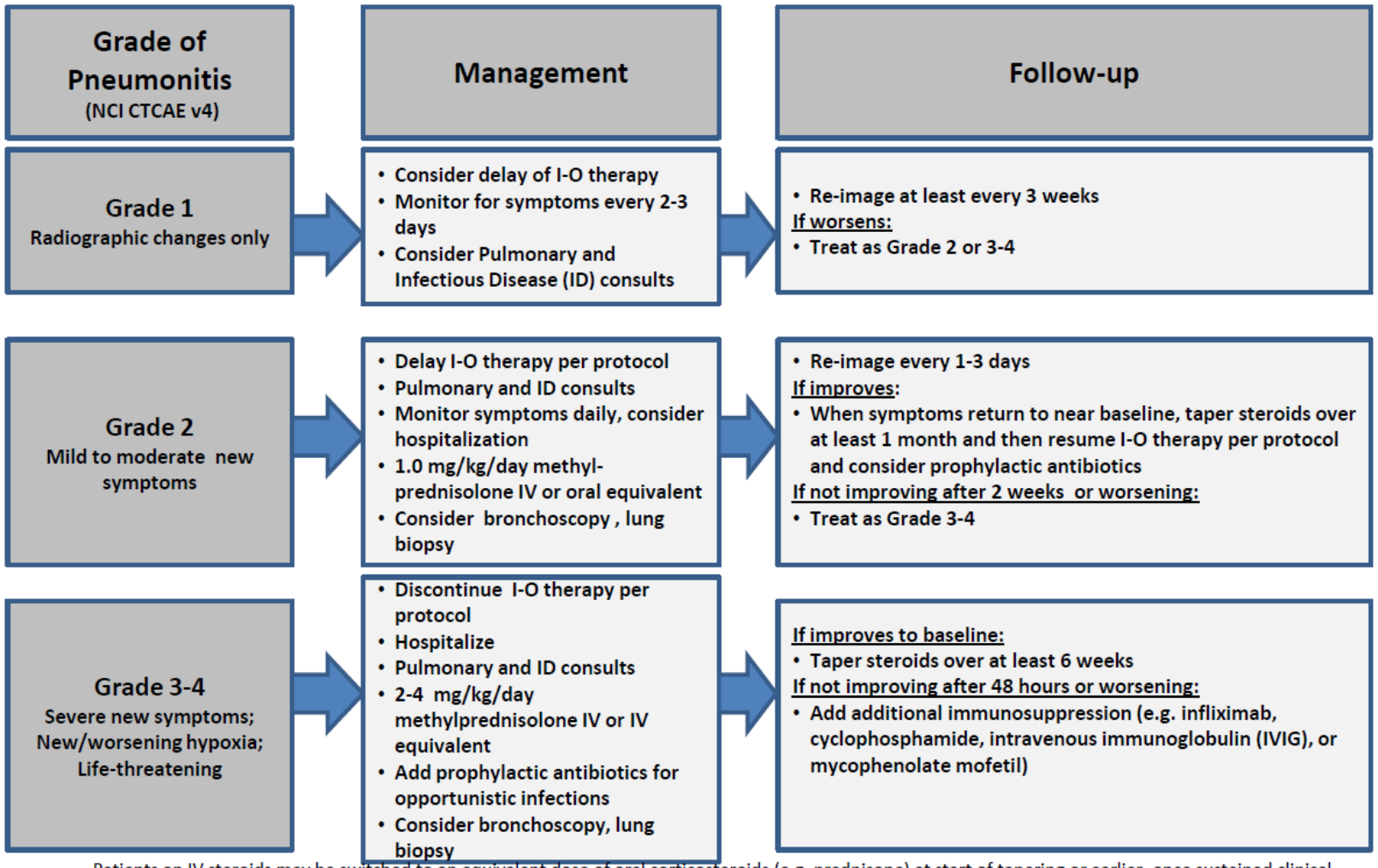
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

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

Pulmonary Adverse Event Management Algorithm

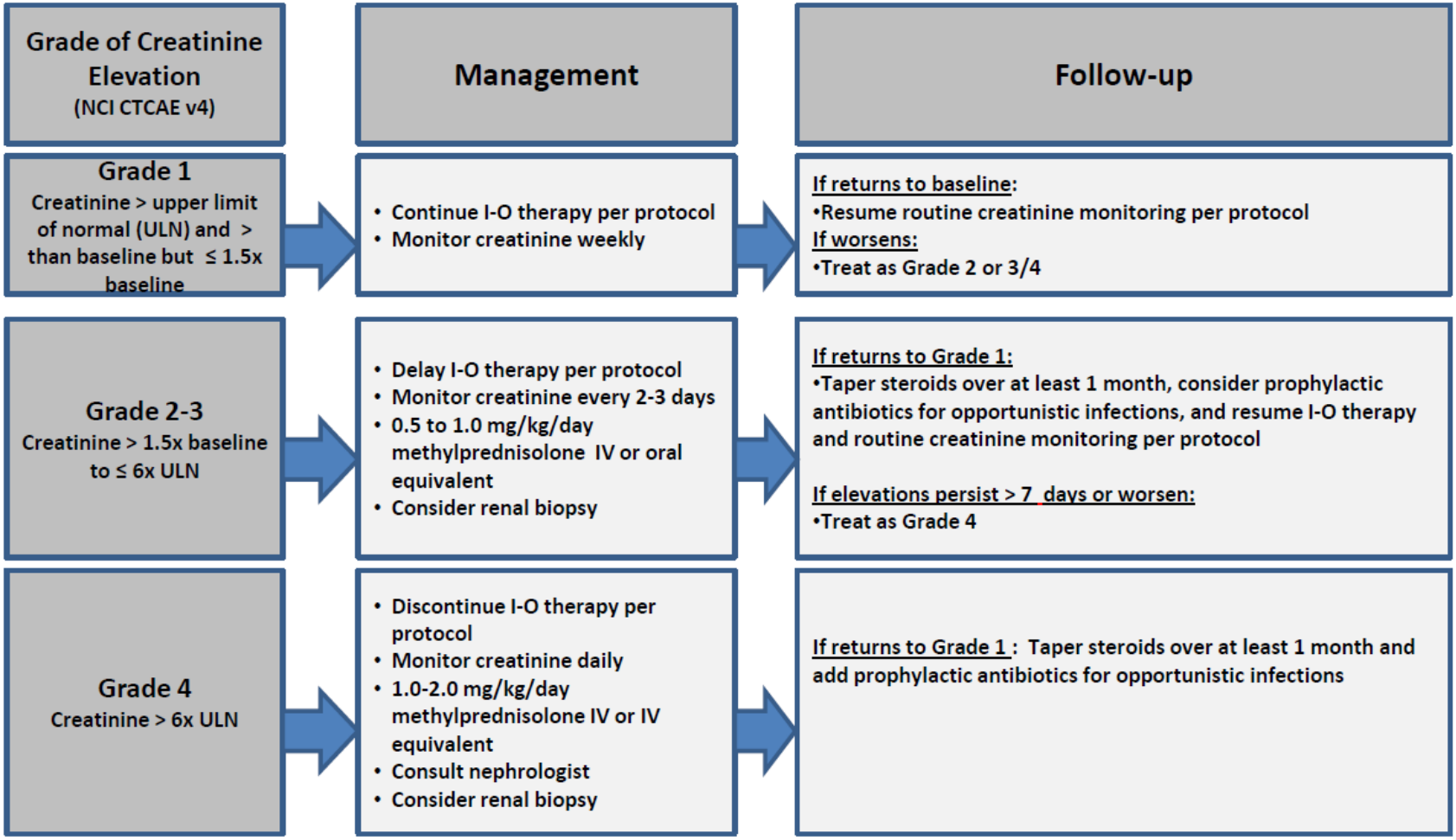
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

Renal Adverse Event Management Algorithm

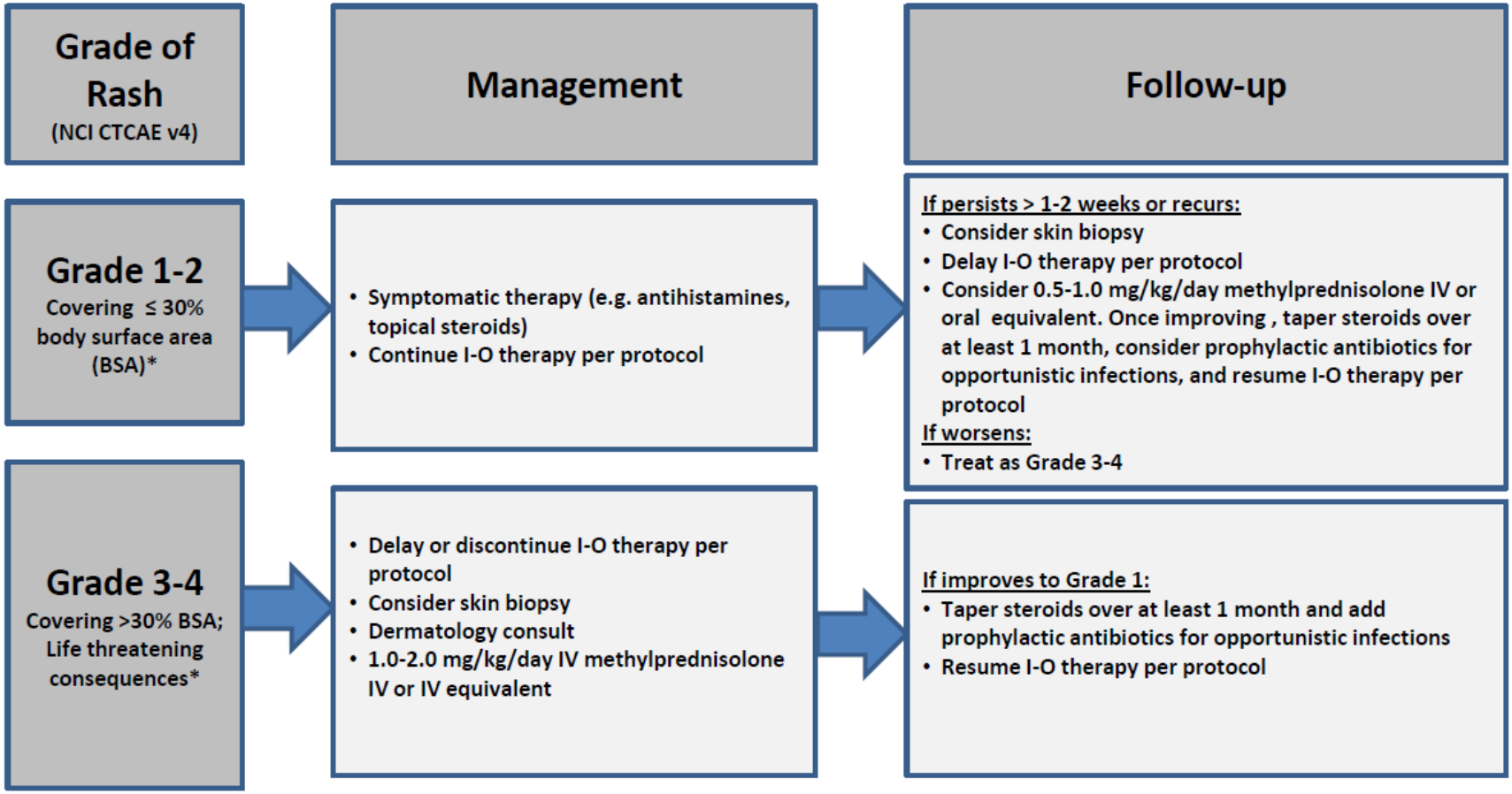
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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

Skin Adverse Event Management Algorithm

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



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.

APPENDIX E: SPECIMEN CHECKLIST AND SHIPPING INSTRUCTIONS

***** PLEASE AVOID DRAWING OR SENDING SPECIMENS ON FRIDAYS AND HOLIDAYS*****

Kit Contents:

- Small Styrofoam box and cardboard mailing sleeve
- Patient Information Form
- FedEx Airbill with pre-printed return address
- 6ml ACD (yellow top) collection tubes
- 10ml Red Top collection tubes
- Absorbent tube holder
- Zip lock specimen bag

To Order Kits:

Participating sites may obtain kits by e-mailing Kim Henderson at Henderson.Kimberly@mayo.edu. E-mail requests should include the site address, contact information and number of kits being requested. Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. Allow 3 to 4 business days to receive the kits.

Packing and Shipping Instructions:

1. Collect Peripheral blood as below (**NOTE:** All kits will contain two 6ml ACD tubes and three 10ml Red top tubes. Each site will determine the appropriate tubes to collect per time point):

Group 1 (without crossover):

- **Baseline:**
  - 12 ml in two (2) ACD tubes
  - 30 ml in three (3) Red Top tubes
- **C1D1, C2D1, C3D1:**
  - 12 ml in two (2) ACD tubes
  - 20 ml in two (2) Red Top tubes
- **C1D15, C2D15, C3D15:**
  - 12 ml in two (2) ACD tubes
  - 10 ml in one (1) Red Top tube
- **C4D1, EOT, Safety Follow-Up:**
  - 10 ml in one (1) Red Top tube

Group 1 (with crossover):

- **Baseline: same as Group 1 without crossover**
- **C1D1, C2D1, C3D1: same as Group 1 without crossover**
- **C1D15, C2D15, C3D15: same as Group 1 without crossover**
- **C4D1: same as Group 1 without crossover**

- **Before first 4 doses of CDX-1127 (varlilumab):**
  - 10 ml in one (1) Red Top tube
- **EOT, Safety Follow-Up:**
  - 20 ml in two (2) Red Top tubes

Group 2:

- **Baseline, C1D1, C2D1, C3D1**:
  - 12 ml in two (2) ACD tubes
  - 30 ml in three (3) Red Top tubes
- **C1D15, C2D15, C3D15:**
  - 12 ml in two (2) ACD tubes
  - 10 ml in one (1) Red Top tube
- **C4D1, EOT, Safety Follow-Up:**
  - 20 ml in two (2) Red Top tubes

2. All specimens are to be clearly labeled with the protocol MC168D, the patient's initials (last, first, middle), study patient ID number (if available) and date of collection.
3. Place the tubes in the absorbent holder and seal in the zip lock specimen bag.
4. Place the filled specimen bag in the Styrofoam container.
5. Loosely pack with paper toweling.
6. Place the Styrofoam container and Patient Information form within the cardboard mailing sleeve.
7. Prepare the package for shipping, applying packing tape as needed. Adhere the Fed Ex Airbill to the exterior of the box. Ship specimens via priority overnight delivery (next day delivery by 10am) the same day collected.
8. Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location.

Please e-mail Kim Henderson at Henderson.kimberly@mayo.edu to notify the laboratory when samples are being shipped. Indicate the protocol number MC168D, the Fed Ex tracking number, name and phone number of the contact person. The samples should be shipped to the following:

Mayo Clinic
Attn: Kim Henderson
221 4th Avenue SW
613 Stabile
Rochester, MN 55905

Patient Information Form

Specimen Date: / /

Patient Initials (last name, first name):

Mayo Clinic Number:

Protocol #: MC168D

Contact Person:

Institution:

Address:

City State Zip

Phone #:

Please indicate which peripheral blood samples are being shipped at this time:

1. Baseline
2. Cycle 1 Day 1
3. Cycle 1 Day 15
4. Cycle 2 Day 1
5. Cycle 2 Day 15
6. Cycle 3 Day 1
7. Cycle 3 Day 15
8. Cycle 4 Day 1
9. End of Treatment
10. Safety Follow-up
11. Before first 4 doses of CDX-1127 (Group 1 crossover ONLY)

For any questions concerning these samples or to obtain blood collection kits for the MC168D study, please contact:

Kim Henderson
Mayo Clinic
(507)284-3805
Henderson.kimberly@mayo.edu

APPENDIX F: PANEL FOR CYTOF ANALYSIS

Target		Clone	Metal Tag
1.	**CD45**	HI30	89Y
2.	**CD196 (CCR6)**	G034E3	141Pr
3.	**CD11a**	HI111	142Nd
4.	**CD5**	UCHT2	143Nd
5.	**CD195 (CCR5)**	NP-6G4	144Nd
6.	**CD4**	RPA-T4	145Nd
7.	**CD8a**	RPA-T8	146Nd
8.	**CD7**	CD7-6B7	147Sm
9.	**CD16**	3G8	148Nd
10.	**CD25 (IL-2R)**	2A3	149Sm
11.	**CD223 (LAG3)**	874501	150Nd
12.	**CD278, ICOS**	DX29	151Eu
13.	**TCRgd**	11F2	152Sm
14.	**CD45RA**	HI100	153Eu
15.	**TIM-3**	F38-2E2	154Sm
16.	**CD183 (CXCR3)**	G025H7	156Gd
17.	**CD194 (CCR4)**	205410	158Gd
18.	**CD197 (CCR7)**	G043H7	159Tb
19.	**CD28**	CD28.2	160Gd
20.	**CD274 (PD-L1)**	29E.2A3	161DY
21.	**CD69**	FN50	162Dy
22.	**CD56 (NCAM)**	NCAM16.2	163Dy
23.	**CD161**	HP-3G10	164Dy
24.	**CD45RO**	UCHL1	165Ho
25.	**CD44**	BJ18	166Er
26.	**CD27**	O323	167Er
27.	**CD30**	BerH8	168Er
28.	**CD19**	HIB19	169Tm
29.	**CD3**	UCHT1	170Er
30.	**CD185 (CXCR5)**	51505	171Yb
31.	**CD273 (PDL2)**	24F.10C12	172Yb
32.	**HLA-DR**	L243	174Yb
33.	**CD279 (PD-1)**	EH12.2H7	175Lu
34.	**CD127 (IL-7R)**	A019D5	176Yb