Document Coversheet

Study Title:

A Phase 1 Study of DEC205mAb-NY ESO 1 Fusion Protein (CDX-1401) given with Adjuvant Poly-ICLC in Conjunction with 5-Aza-2'deoxycytidine (Decitabine) and Nivolumab in Patients with MDS or Low Blast Count AML

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Confidentiality Statement

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1 OBJECTIVES

1.1 Primary Objective

- Evaluate the safety of NY-ESO-1 vaccination (Anti-DEC-205-NY-ESO-1 fusion protein + poly-ICLC) given in combination with decitabine 20 mg/m^2 intravenously and nivolumab 3 mg/kg in patients with MDS or low blast count AML.

1.2 Secondary Objective

- Assess immune and molecular epigenetic responses following combination therapy with nivolumab, decitabine and NY-ESO-1 vaccination.

1.3 Exploratory Objectives

- To record the response rate (Complete Response, Partial Response and Hematological Improvement) in MDS or low blast count AML patients treated with the combination in order to provide descriptive characteristics.
- To record the Overall Survival (OS), Progression Free Survival (PFS) and time to AML transformation (TTT) (for patients with MDS at diagnosis) enrolled on the study.

2 BACKGROUND

2.1 Myelodysplastic Syndrome

Myelodysplastic Syndrome (MDS) is a hematologic disorder of adults, with an estimated overall incidence of 5 cases per 100,000 people annually in the United States (1). MDS is characterized by ineffective hematopoiesis with progressive cytopenias and a variable risk of transformation to acute myeloid leukemia (AML) (2). For patients with intermediate-2 (Int-2) or high-risk disease as defined by the International Prognostic Scoring System (IPSS) (a designation which includes patients with low blast count AML (<30% blasts) for the purpose of this study), the median overall survival (OS) is 1.2 years or 0.4 years, respectively, and these patients have a high risk of transformation to high-blast count AML (3). The goal of therapy for these patients is, therefore, to modify the natural history of the disease and extend the survival and time to AML transformation (>30% blasts). With the exception of allogeneic stem cell transplantation (SCT), for which most patients are unsuitable due to age and comorbidities, there is currently no curative treatment for MDS.

Development of specific MDS treatments has been challenging not only due to limitations of treatment tolerance, but also by the frequent unfavorable biological features of the malignant clone which include adverse cytogenetics, limited normal stem cell reserve, and higher levels of multidrug resistance. The development of non-intensive “epigenetic” therapy with azanucleosides like azacitidine and decitabine, so called hypomethylating agents (HMAs), has been driven by the goal of "re-programming" growth and differentiation, rather than eradication by cytotoxic effects, of the abnormal cells and this strategy has been the first to demonstrate a survival advantage in patients with MDS (4). Unfortunately, responses to this therapy are relatively short lived, lasting months to years, and following disease progression on these treatments survival is dismal on the order of 4-6 months (5).

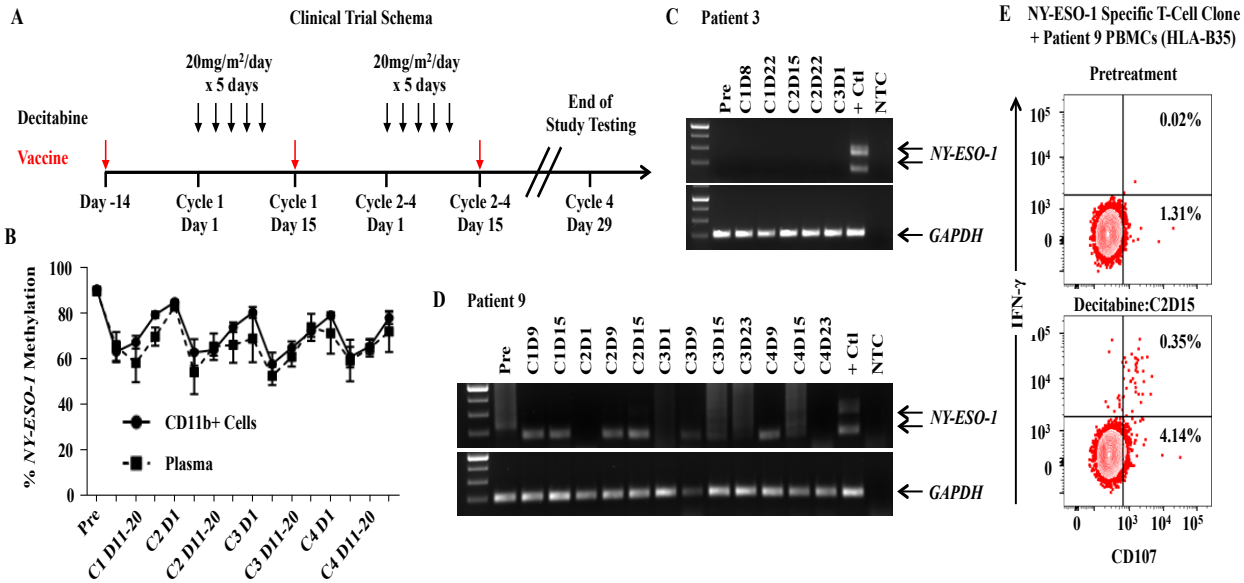
The mechanism(s) responsible for response to HMAs therapy remain a matter of some debate. Historically, cytotoxicity or re-expression of epigenetically silent tumor suppressor genes were thought to be critical to response, but recent work suggests that immunological mechanisms may play a role (6). HMAs have been adopted as the standard of care for treatment of patients with MDS and select patients with AML, but despite multiple attempts to combine them with other agents, responses have not been pushed substantially beyond the originally described40% rate.

2.2 NY-ESO-1 Vaccination Trial

Recent advances in cancer immunotherapy led us to develop a novel approach that utilizes the ability of HMAs to induce expression of tumor antigens that can be exploited to unleash the anti-tumor potential of the immune system.

We previously showed that AML/MDS patients receiving HMAs demonstrate increased expression of the immunogenic tumor antigen NY-ESO-1 (7). Induction of NY-ESO-1 expression occurred in both clinical responders and non-responders to HMAs, and was sufficient to induce cytotoxicity in HLA-compatible T-cells recognizing NY-ESO-1. This data provided the rationale for our recently completed phase I study combining NY-ESO-1 vaccination with decitabine in patients with MDS or low blast count AML (**Figure 1A**). In all, 9 patients of median age 64 years were enrolled and treated on protocol (**Table 1**). The most frequently observed adverse events, related to decitabine and the underlying hematological malignancy, included cytopenias (predominantly grades 3/4), elevated liver enzymes (grade 3), fatigue (grade 2), edema (grade 2/3) and diarrhea (grade 1/2) (**Table 2**). Two patients did not complete four cycles of therapy due to serious adverse events; one patient with a history of myocardial infarction (MI) developed in-stent restenosis and recurrent MI; a second patient suffered a terminal intracranial hemorrhage due to thrombocytopenia (deemed decitabine related).

Figure 1 Summary of Prior Study Results



Patients demonstrated the expected transient effects on both global and NY-ESO-1 specific methylation (**Figure 1B**). Importantly, the methylation signature from CD11b selected peripheral blood cells was recapitulated entirely in the plasma cell free DNA harvested from patients, allowing us the opportunity to use cell free DNA rather than cells to assess changes in DNA methylation in future studies. A majority of patients treated on this study demonstrated induced expression of NY-ESO-1 in circulating CD11b selected cells (exemplar patients demonstrated in **Figure 1C** and **Figure 1D**) and developed NY-ESO-1 specific T-cell (exemplar in **Figure 1E**) responses but this response was relatively small compared to the historical use of this vaccine in patients with solid tumors (**Table 3**) (8)

Table 1 Demographics

	n = 9
Age	64 (57-71 yr)
Male	6 (67%)
Female	3 (33%)
Diagnosis	2 AML (22%); 7 MDS (78%)

Table 2 Adverse Events

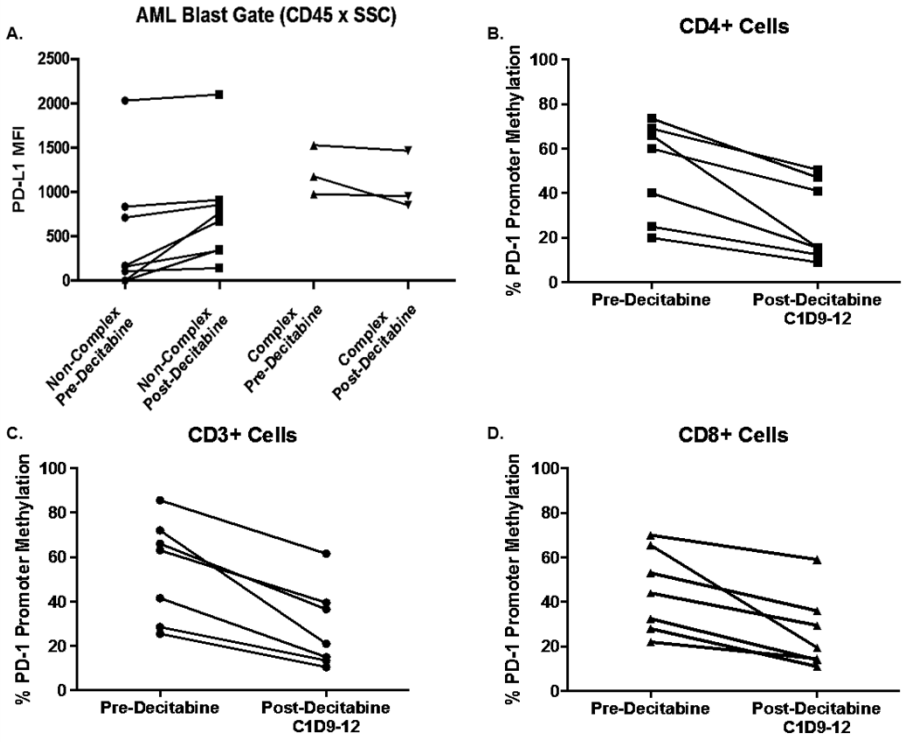
n = 9	All Grades	Grade ≥3
Cytopenias		
Anemia	5	4
Thrombocytopenia		6
Neutropenia		6
Hyperbilirubinemia	5	1
LFT Elevation	8	0
Diarrhea	4	0
Fatigue	4	0
Edema	4	1

Table 3 Correlation of Vaccine Response with Induced NY-ESO-1 Expression

Patient	Antibody Titer		CD4 response		CD8 response		NY-ESO-1 expression	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	-	-	+ (1)	- (0)	- (0)	++ (3)	-	-
2	-	+	++ (2)	+++ (3)	- (0)	+ (1)	-	+
3	-	-	- (0)	+ (2)	- (0)	- (0)	-	-
4	-	-	- (0)	+ (2)	- (0)	+ (1)	-	+
5	-	-	- (0)	+ (1)	- (0)	- (0)	-	+
6	-	-	- (0)	+ (1)	- (0)	+ (2)	+	+
7	-	-	- (0)	+ (1)	- (0)	- (0)	-	+
8	-	-	- (0)	- (0)	- (0)	- (0)	-	+
9	-	++	+++ (1)	++++ (4)	- (0)	+++ (3)	-	+

We and others have demonstrated that PD-L1 is expressed on CD34+ myeloid cells from patients with MDS and AML (7, 9) (**Figure 2)**. Previous studies have demonstrated that NY-ESO-1+ tumor infiltrating lymphocytes express the immune checkpoint protein PD-1. In addition, PD-1 expression is induced in lymphocytes of AML/MDS patients receiving decitabine [(7) and unpublished]. These results provide a rationale for the inclusion of the PD-1 inhibitor nivolumab in combination with our vaccine approach.

Figure 2 A) PD-L1 expression on AML blasts; B-D) PD-1 hypomethylation in lymphoid cells from patients receiving decitabine.



In this Phase 1 study we propose to combine our backbone NY-ESO-1 vaccination/decitabine approach with the PD-1 checkpoint inhibitor nivolumab in HMA naïve, non-transplant eligible, MDS patients. We hypothesize that the addition of nivolumab to our combination of standard-dose

decitabine and NY-ESO-1 vaccination will improve the qualitative and quantitative antigen specific CD4+ and CD8+ T-cell response to NY-ESO-1 vaccination in MDS patients. We will use this study to test this hypothesis with the three specific objectives as described in 1.0.

2.3 Study Drugs

2.3.1 Vaccine (Anti DEC-205-NY-ESO-1 Fusion Protein (CDX-1401)/ Poly ICLC)

DEC205mAb-NY ESO 1 fusion protein is being developed by Celldex Therapeutics, Inc, under the code designation CDX-1401. CDX-1401 is a fusion protein consisting of a fully human monoclonal antibody (HuMab) of IgG1 (kappa) isotype with specificity for the dendritic cell receptor, DEC-205, genetically linked to the full length NY-ESO-1 tumor antigen (Ag) protein (10). A letter of authorization to refer to the Celldex IND 14090 for relevant data on clinical studies with CDX-1401 will be provided with this submission and a companion IND for the use of this protein in this trial will be filed prior to the opening of this study.

The cancer-testis (CT) antigen NY-ESO-1 is expressed in a wide range of different tumor types, but its expression in normal adult tissues is limited to the testis (11, 12). It has been shown that NY-ESO-1 is highly immunogenic and able to induce spontaneous immune responses in patients with NY-ESO-1–expressing tumors but not in healthy individuals (13). Furthermore, the presence of a spontaneous anti–NY-ESO-1 antibody (Ab) response is typically associated with spontaneous NY-ESO-1–specific CD8+ and CD4+ T cell responses in melanoma patients (14-16). Because of its frequent expression in tumors and high immunogenicity, NY-ESO-1 has been an attractive target for cancer immunotherapy and has been used in a series of clinical vaccine trials, although it has not been evaluated in MDS since the antigen is not spontaneously expressed in this malignancy (17, 18).

Extensive immune monitoring during a variety of studies has revealed that NY-ESO-1–specific immune responses are inducible by a variety of NY-ESO-1–based vaccines such as HLA class I and/or class II-binding peptides, recombinant viruses, and recombinant protein with or without adjuvants or delivery systems, even in patients without spontaneous immunity (19-24). Compared to vaccination with HLA-binding short peptides, vaccination with full-length tumor Ag such as recombinant proteins or viruses is considered to be more attractive because of the potential to induce a wider repertoire of specific Ab and T cell responses. Furthermore, recombinant proteins or viruses are expected to induce high-avidity T cells, whereas short peptide vaccination often induces low avidity T cells that fail to recognize naturally processed Ag (25, 26). Full-length tumor Ags intrinsically contain all possible CD4+ and CD8+ T cell epitopes for any type of HLA allele and thus they should potentially activate both CD4+ and CD8+ T cell subsets. However, it was found that vaccination with recombinant NY-ESO-1 protein in the presence of vaccine adjuvant, bacillus Calmette-Gue´rin plus GM-CSF or imiquimod, induced CD4+ T cell responses in most immunized patients, whereas cross-priming of NY-ESO-1–specific CD8+ T cells was rare unless NY-ESO-1 protein was formulated in ISCOMATRIX or strong adjuvant like CpG was used (19, 23, 24, 27). In contrast, vaccination with recombinant viruses inducing intracellular NY-ESO-1 expression elicited frequent CD8+ T cell responses, though not always accompanied by the induction of specific CD4+ T cells (10). These observations are consistent with distinct pathways for MHC class I and class II Ag presentation and thus for separate processing and presentation of endogenous and exogenous protein via MHC class I and class II, respectively. Because both tumor Ag-specific CD8+ and CD4+ T cells cooperatively play important roles in eradicating cancer (28),

using vaccine constructs that can simultaneously activate NY-ESO-1–specific CD8+ and CD4+ T cells is a much desired strategy to immunologically reverse the clinical course of cancer.

Preclinical Studies with CDX-1401

The DEC-205 receptor has been shown to be an efficient mAb-based target to enhance the induction of strong Ag-specific immune responses and cross-presentation in mice (29) and humans (30). The receptor is also expressed on human monocyte-derived dendritic cells (DCs) along with other endocytic receptors, such as the mannose receptor/CD206 and DC-SIGN/CD209 [reviewed in (30)]. In a recent study at Roswell Park Cancer Institute, full-length NY-ESO-1 was fused to the C terminus of human anti-DEC-205 (DEC205mAb-NY-ESO- 1 fusion protein) (10). Whereas non-targeted and antibody-targeted NY-ESO-1 proteins similarly activated CD4+ T-cells, cross-presentation to CD8+ T-cells was only efficiently induced by targeted NY-ESO- 1 (10). In addition, DEC-205 targeting elicited specific CD4+ and CD8+ T-cells from peripheral blood lymphocytes of cancer patients. In this study, the DEC-205 mAb-NY-ESO-1 fusion protein will be directly injected subcutaneously in an effort to prime endogenous DCs with full length NY-ESO-1 full length protein and thereby sensitize the immune system to NY-ESO-1 induced in MDS cells following exposure to decitabine and nivolumab. Our previously completed phase I study has demonstrated that the combination of NY-ESO-1 vaccination with decitabine is safe.

A detailed discussion of the preclinical pharmacology, pharmacokinetics, and toxicology of Anti DEC-205-NYESO-1 Fusion Protein can be found in the Celldex Investigator's Brochure.

Poly-ICLC

Poly-ICLC (Hiltonol, manufactured by Dalton for Oncovir, Inc., to be provided by Celldex Therapeutics) is an experimental viral mimic and broad activator of innate immunity. While initially developed as an interferon inducer, poly-ICLC has much broader biological effects in humans, including specific antiviral, immune activating, vaccine adjuvant, and antitumor actions.

Synthetic double stranded RNA (dsRNA) such as poly-IC, which consists of a pair of strands of poly-inosinic and poly-cytidylic acids, are not normally found in mammalian cells, but they are the basic genetic material or are replication byproducts of many viruses (31). Plain Poly-IC itself proved to be ineffective in primates because it is rapidly inactivated by natural enzymes in the blood. However stabilized poly-IC with poly-lysine is a very stable dsRNA that is a potent interferon inducer in man. Early, short term, high dose cancer trials showed that high dose poly-ICLC could induce very large amounts of interferon production in man, but with only modest therapeutic effects and moderate transient toxicity (31). Low dose poly-ICLC is a potent clinical activator of a variety of host defense mechanisms that go well beyond simple induction of interferons and which include reversal or preemption of certain viral or tumor induced inhibitions, broad immune stimulation, gene regulatory and specific antiviral, and anticancer effects, with little or no toxicity (31, 32).

In this study low dose poly-ICLC will be used as a direct immune-enhancer in order to activate T-cells, natural killer cells, and, dendritic cells, release of cytokines such as interferons, interleukins, corticosteroids, and tumor necrosis factor (TNF). Its recently demonstrated effect on dendritic cells through Toll-like receptors (TLR3) may be especially important since CDX-1401 directly targets these cells (33). As described above, dendritic cells play a critical role in the immune response by recognizing pathogens and presenting their antigens to the immune system. The poly-ICLC used

in this study will provide an adjuvant effect for the CDX-1401 with increased antibody and cellular immune response to NY-ESO-1antigen.

Clinical Studies with CDX-1401 and adjuvants

One open-label, dose-escalation study (Protocol CDX1401-01) has been conducted with CDX-1401 (8). In this trial, 45 patients with treatment refractory solid tumors were treated with CDX-1401 (0.1 to 3 mg) in combination with the TLR7/8 agonist, resiquimod (applied topically or injected subcutaneously); the TLR 3 agonist poly-ICLC (injected subcutaneously); or both TLR agonists. Treatment was administered over ~6 weeks of a 12-week cycle, with repeated 12-week cycles if tolerated in the absence of progression. Treatment was well-tolerated with no dose-limiting toxicity (DLT). Administration site reactions (erythema, pain, pruritus, rash, induration, swelling; mild in nearly all cases) were frequent, occurring in 78% of the patients. Additional adverse events thought potentially related to treatment included fatigue (24%), nausea (9%), chills (9%), decreased appetite (7%), influenza like illness (7%), arthralgia (7%) and myalgia (7%). No Grade 3, 4 or 5 events were reported as potentially related to study treatment. Thirteen patients had stable disease, with a median duration of 6.7 months (range = 2.4+ to 13.4). Four patients had measurable tumor shrinkage (% shrinkage of the sum of the diameters of target lesions = -2, -8, -20 & -21%). Significant anti-NY-ESO-1 titers (up to 1:800,000) occurred in 80% of patients. Approximately 60% of patients with NY-ESO-1+ tumors had significant anti-NY-ESO-1 titers at baseline and most increased after vaccination. Humoral responses were elicited in both NY-ESO-1 positive and negative patients. NY-ESO-1-specific T cell response (IFN-γ ELISPOT) was absent or low at baseline, but increased post-vaccination in approximately half of the patients. Evidence of NY-ESO-1 specific CD4 or CD8 T cell responses were observed using intracellular cytokine secretion and pentamer analysis in selected samples. Similar immune responses were observed with adjuvants, individually or in combination, with no clear dose response in these small cohorts. Interestingly, 5 of 8 patients treated with checkpoint inhibitors within 3 months of CDX-1401 administration reportedly had objective tumor regression (CDX 1401 Investigator Brochure, 2013). In conclusion, preliminary data from study CDX-1401 show that dendritic cell targeting through DEC-205 can safely lead to robust humoral and cellular immunity when combined with TLR agonists in cancer patients. Results provide the basis for further study, including novel combination immunotherapy strategies such as that involving checkpoint blockade.

2.3.2 Nivolumab

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.1 Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. 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. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration. OPDIVO™ (nivolumab) is approved for use in multiple countries including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

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, 2013). 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 (34), renal (35-37), esophageal (38), gastric (39), ovarian (40), pancreatic (41), lung (42), and other cancers (Nivolumab 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.

Nivolumab monotherapy is approved in multiple countries, including the US and EU, for unresectable or metastatic melanoma, previously treated metastatic NSCLC, and previously treated advanced RCC; it is also approved for the treatment of cHL and urothelial carcinoma in the US. In addition, nivolumab has been approved for use in combination with ipilimumab for unresectable melanoma in multiple countries, including the US and EU.

Clinical Safety

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 12,300 subjects treated to date (Nivolumab Investigator Brochure, 2016). For monotherapy, the safety profile is similar across tumor types. There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. In Phase 3 controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical efficacy, and manageable using established safety guidelines. Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and timely immunosuppressive therapy or other supportive care. In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored.

Combinations with HMAs in Myeloid Malignancy

Although limited activity was previously shown for single agent PD-1 blockade in patients with active myeloid malignancy (43), recently authors at the MD Anderson Cancer Center reported preliminary results from two studies suggesting that combinations of PD-1 blockade with hypomethylating drugs may have substantial activity (44-46).

The first of these studies reported on 66 patients with relapsed or refractory AML (median number of prior regimens 2, range 1-7). Patients received standard dose/schedule azacitidine (75 mg/m^2 x 7 days) in combination with nivolumab at 3 mg/kg every 2 weeks given on days 1, 14 of each cycle. Courses were repeated indefinitely every 4-5 weeks and patients were deemed eligible for response assessment if they had received at least 3 cycles of therapy. Six patients were initially enrolled to a safety cohort and only 1 had a dose limiting toxicity (grade 3 pneumonitis) thus this dose/schedule was declared the recommended phase 2 dose and to date an additional 60 patients have been accrued and treated. At the 2017 EHA meeting in June, 63 patients were eligible for response assessment and these included 14 patients who have demonstrated CR or CR with incomplete count recovery (3;11; 22%), 7 hematological improvements (11%). Responses were observed after a median of 2 courses. Early mortality at 4 and 8 weeks was observed in 5 and 11% of patients respectively. Immune toxicities were observed in 15 (23%) patients with grade 3 or 4 events seen in 8 patients (12%) and grade 2 events in 7 patients. The most frequently reported grade 3 or 4 events were pneumonitis, colitis, nephritis, skin rash and hypophysitis. One patient died related to pneumonitis, the remaining 14 patients were managed with steroids and 13 of them were retreated with nivolumab. Immune toxicities presented both early and late (range 4 days to 3.5 months). Responses in this cohort were compared favorably with the historical response to salvage therapy in this population at MD Anderson.

The second study was recently updated at the 2017 EHA meeting and presented by Dr. Garcia-Manero and colleagues reported on 63 patients with MDS either previously untreated or relapsed after HMA failure (45). The study design allowed previously untreated patients to receive upfront azacitidine at a dose of 75 mg/m2 sq x 5 days with either nivolumab 3 mg/kg IV on day 6 and 20 of each cycle, ipilimumab 3 mg/kg IV on day 1 of a 21 day cycle or nivolumab 3 mg/kg IV on days 1 and 15 in combination with ipilimumab 3 mg/kg IV on day 1 of a 28 day cycle. Patients who had previously failed an HMA were randomized receive either single agent nivolumab 3 mg/kg IV days 1 and 15, single agent ipilimumab 3 mg/kg IV on day 1 of a 21 day cycle or nivolumab 3 mg/kg IV on days 1 and 15 in combination with ipilimumab 3 mg/kg IV on day 1 of a 28 day cycle. After 6 cycles of the checkpoint inhibitors, patients were allowed to resume azacitidine if there had been no response or disease progression. A maximum of 20 patients may be enrolled to each cohort for a total of 180 patients potentially enrolled to study. At the time of abstract presentation, 63 patients had been enrolled with 2 screen failures. At the time of the most recent update, 54 (86%) patients were evaluable for response and toxicity including 21 previously untreated MDS patients who received azacitidine in combination with nivolumab, and 15 and 18 patients who had previously failed a hypomethylating agent who received single agent nivolumab or ipilimumab respectively. The median age for enrolled patients to date is 69 years (range 39-85). Median number of treatment cycles is 3 with a range of 1 to 11. Related grade > 3 non-hematologic AEs have been reported in 3 (27%) pts in the azacitidine + nivolumab cohort, 6 (40%) in the single agent nivolumab cohort, and 3 (33%) in the single agent ipilimumab cohort, thus the stopping rule for toxicity was not met in any cohorts. Delays of therapy due to adverse events were required in 9 patients. These adverse events were reported as rash (N=1), adrenal insufficiency (N=1), colitis (N=1), thyroiditis (N=2), pneumonitis (N=3), and nephritis (N=1). A previous report from this cohort described the most commonly reported ≥ Grade 3 adverse events in the combination arm in 11 patients (45 hemorrhage, hyperglycemia, fever and elevated LFTs (in 9% each). Commonly reported AEs irrespective). These included pulmonary infections (seen in 18% of patients), followed by intracranial of attribution in these patients of any grade included constipation and maculopapular rash in 45%, nasal congestion in 36%, arthralgia, cough, and stomach pain in 27% each, diarrhea, edema, fatigue, hyperkalemia, and insomnia in 18%, and anorexia, dyspnea, GERD, hyperglycemia, hyponatremia, hypotension, mucositis, nausea, pneumonitis, and weight loss in 9%.Early mortality was reported in 1 patient (at the 8 week time point) due to a non-related intracranial hemorrhage. The response rate in the previously untreated cohort who received azacitidine + nivolumab was reported as 62% (13/21) with 6 patients reported to have CR. Nivolumab as a single agent had a 0% response rate (thus this arm has been stopped) and single agent ipilimumab was reported to produce responses in 5/18 patients (30%).

These data support the safety and tolerability of combination strategies using nivolumab and HMAs in patients with myeloid malignancy. We would predict that the present combination strategy would have a similar toxicity profile and will adopt the best practice with respect to aggressive management of immune related adverse events.

2.3.3 Decitabine

Decitabine is known to be well tolerated, with a favorable extramedullary toxicity profile and infrequent treatment-related mortality. Decitabine is a nucleoside analog that is unsuitable for methylation due to the replacement of carbon with nitrogen at the 5’ position of the pyrimidine ring. Decitabine is activated intracellularly by deoxycytidine kinase and other nucleotide kinases to the active metabolite 5-aza-2’-deoxycytidine-triphosphate (5-aza-2 ’-dCTP) that can be

incorporated into DNA during the S-phase of the cell cycle and forms irreversible covalent bonds with DNA methyltransferases (DNMT) at cytosine sites targeted for methylation (32). Decitabine is believed to exert its antineoplastic effects by inhibition of DNA methyltransferases, causing DNA hypomethylation and activation of genes involved in differentiation or apoptosis. Decitabine was the first drug to demonstrate significant activity against MDS and has been shown to induce transfusion independence for red blood cells and platelets as well as improvements in neutropenia (47).

Based upon these results decitabine was approved by the US food and drug administration for all MDS subtypes in 2006 and it remains a frequent standard approach to the treatment of patients with MDS (2). It has been hypothesized that low dose, prolonged exposure to decitabine correlates with clinical response as a result of changes in gene expression induced by a reduction in DNA methylation; rather than cytotoxicity which occurs with higher doses of decitabine (48). Recently we and others have shown that exposure of myeloid cells to decitabine and azacitidine (an analog of decitabine which incorporates into both DNA and RNA), can induce expression of CT antigens when given in vitro to AML cell lines, and further that patients treated with these drugs can induce expression of some CT antigens as well (17, 18, 49).

2.4 Rationale

The hypomethylating agents (HMAs) azacitidine and decitabine are the standard of care for the treatment of myelodysplastic syndromes (MDS) but only about 40% of patients respond. We have demonstrated that AML/MDS patients receiving HMAs express the immunogenic tumor antigen NY-ESO-1 in circulating CD34+ blasts after treatment in both clinical responders and non-responders. These data provided the rationale for our recently completed phase I study combining NY-ESO-1 vaccination with decitabine in newly diagnosed MDS patients. Nine patients, all at the Roswell Park Cancer Institute, were enrolled and treated on our study. A majority of the treated patients developed NY-ESO-1 specific T-cells in response to vaccination, but these were less robust than the responses observed in patients with solid tumors who got the same vaccine. We and others have shown that PD-L1 is expressed on myeloid cells from patients with MDS and AML (7, 9) and further, that that expression of the immune checkpoint protein PD-1 is induced in lymphocytes from AML/MDS patients receiving decitabine. Based on these results, we propose a Phase 1 study that adds the PD-1 inhibitor nivolumab to our backbone combination of standard-dose decitabine and NY-ESO-1 vaccination in HMA naïve, non-transplant eligible, MDS patients and low blast count AML patients. We will test the hypothesis that the addition of nivolumab will improve the qualitative and quantitative antigen specific CD4+ and CD8+ T-cell response to NY-ESO-1 vaccination in MDS/AML patients.

3 INCLUSION AND EXCLUSION CRITERIA

3.1 Inclusion Criteria

Subjects who present with a suspected or confirmed diagnosis of MDS/AML, and who are interested in potential participation on a clinical trial, will be screened for enrollment. Only patients who are willing to sign a written informed consent form will be screened. Patients must undergo bone marrow aspirate and biopsy with sample acquisition for protocol screening.

To be included in this study, participants must meet the following criteria:

1. Have a confirmed diagnosis of:

a. IPSS intermediate-1, intermediate-2 or high-risk MDS including Chronic Myelomonocytic Leukemia (CMML) **OR**

b. Low blast count AML with ≤ 30% blasts previously classified as Refractory Anemia with excess blasts in transformation.

2. Age ≥ 18 years of age.
3. Have an ECOG Performance Status of ≤ 2. Refer to **Appendix C**.
4. Have adequate organ function defined by the following laboratory values:
    - Hepatic:
        - Total bilirubin ≤ 3 X upper limit of normal (ULN) (except subjects with Gilbert Syndrome, who can have total bilirubin up to 3.5 X ULN)
        - Aspartate Transaminase (AST/SGOT) and Alanine Transaminase (ALT/SGPD) ≤ 3 X ULN
    - Renal:
        - Serum creatinine ≤ 2.5 X ULN
    - Cardiac:
        - Troponin-I, CK-MB≤ ULN
        - LVEF ≥ LLN (institutional limit)
5. Participants of child-bearing potential must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
6. Participant or legal representative must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.
7. No prior exposure to nivolumab.
8. No prior investigational therapy within 2 weeks prior to study enrollment.

Refer to **Appendix A** for the **ELIGIBILITY VERIFICATION FORM: INCLUSION CRITERIA** checklist.

3.2 Exclusion Criteria

Because this study is designed to examine survival as a secondary endpoint we will exclude patients who are eligible for an allogeneic bone marrow transplant at the time of study enrollment. If an enrolled patient subsequently becomes eligible for transplant, they will not be prevented from proceeding to the appropriate clinical treatment indicated.

Participants will be excluded from this study for the following:

1. Subjects with life-threatening illnesses other than MDS, uncontrolled medical conditions or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, or put the study outcomes at risk.
2. AML associated with inv(16); t(16;16); t(8;21) or t(15;17).

3. Previously untreated MDS with isolated del5q (for which lenalidomide is approved an approved therapy) and chronic myelomonocytic leukemia (CMML) with rearrangements of the PDGF receptor (for which imatinib is approved therapy), unless they have previously failed these approaches.
4. Subjects with symptomatic central nervous system (CNS) disease which is not adequately controlled.
5. Subjects who have received prior radiation therapy for extramedullary disease within 2 weeks of first dose.
6. Has known immunosuppressive disease (e.g. HIV, AIDS or other immune depressing disease). Testing is not required, only to be done for a possible diagnosis which is not confirmed.
7. 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. In addition, subjects will be excluded for any of the following:
    - Myocardial infarction or arterial or venous thromboembolic events within 6 months prior to baseline or severe or unstable angina, New York Heart Association (NYHA) Class III or IV disease
    - Active congestive heart failure (New York Heart Association functional classification III or IV).
    - Documented history of cardiomyopathy with EF< 30%.
    - Uncontrolled hypertension (SBP>160/DBP>100 despite medical intervention).
    - History of myocarditis of any etiology
8. Subjects who have hypersensitivity to decitabine, CDX-1401, poly-ICLC or nivolumab.
9. History of auto-immune disease (e.g., thyroiditis, lupus), except vitiligo.
10. Pregnant or nursing female subjects.
11. Unwilling or unable to follow protocol requirements.
12. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive study drug.
13. Regular use of immunosuppressant drugs such as steroids (>20mg prednisone equivalents), azathioprine, tacrolimus, cyclosporine, etc. Use is not permitted within 4 weeks before recruitment.

Refer to **Appendix B** for the **ELIGIBILITY VERIFICATION FORM: EXCLUSION CRITERIA** checklist.

3.3 Special Populations

Only adult patients who are able to provide informed consent will be eligible. Adult patients without capacity, infants and children will be excluded. No pregnant women or prisoners will be eligible for enrollment on this study.

3.4 Inclusion of Women and Minorities

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

4 LOCAL AND STUDY-WIDE NUMBER OF SUBJECTS

A maximum of 18 evaluable participants (minimum of 3) at multiple sites, including RPCI will be enrolled and treated on this study.

5 LOCAL AND STUDY-WIDE RECRUITMENT METHODS

- Potentially eligible patients will be recruited from the population of newly diagnosed MDS patients referred to the protocol investigators. Patients will have a suspected or known diagnosis of MDS or low blast count AML with MDS related changes and be appropriate for therapy with a hypomethylating agent (HMA).
- Patients will be referred to any of the leukemia doctors where the study is open and, will be offered the opportunity to enroll on protocol should they wish to do so. Information regarding this study will be conveyed to local hematologists who see patients with newly diagnosed MDS in a letter approved by the IRB.
- A letter will be distributed to local hematologists/oncologist who sees potentially eligible patients. These physicians can then refer patients to us for consideration of trial participation. The study will be registered on clinicaltrials.gov and RPCI will hold the IND for this study. Patients may review the study on this website or on the RPCI and MDACC external websites.
- All study related advertising documents used at any site will first be reviewed by the RPCI IRB and by the local IRB at any participating institution prior to their use.

6 MULTI-SITE RESEARCH

Refer to **Appendix K**: Instructions for Network Sites.

- The proposed project will be opened initially at Roswell Park Cancer Institute and at one potential additional site. In order to ensure that all patients are treated appropriately and in a consistent fashion we will ensure the following:
    - All sites will have the most current version of the protocol, consent document, and HIPAA authorization.
    - All required approvals (initial, continuing review and modifications) have been obtained at each site (including approval by the site's IRB of record).
    - All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.
    - All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies.
    - All local site investigators will conduct the study in accordance with applicable federal regulations and local laws.

  - All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

- This study will have up to two total sites including RPCI. If the study opens at a second site, the investigators will have a biweekly (i.e., once every 2 weeks) conference call to discuss the results of all patients enrolled and treated on study, otherwise the investigator will review the records of all patients enrolled at least every 2 weeks. At this review the principal investigators will review the following:
  - Problems (inclusive of reportable events).
  - Interim results.
  - The closure of the study according to the described stopping rules below
- As a phase 1 study, all AEs will be reviewed weekly by the Early Phase Clinical Trials committee at RPCI.

7 STUDY TIMELINES

- During the 3+3 component, accrual will be suspended until the three patients in each cohort have completed the DLT window (6 weeks after the last patient has begun therapy).
- Patients will be enrolled and treated on study for as long as they are deriving clinical benefit. Treatment on study has no specified end time.
  - Median progression free survival for patients with MDS receiving hypomethylating agents on clinical trials is between 18 and 24 months.
  - This study is therefore likely to enroll all 18 patients within 2 years and all patients are likely to have completed the study within 7 years of study opening.
- An interim analysis of correlative studies will be performed after every 3 patients have been enrolled and treated on the study for at least 5 months or come off treatment, whichever comes first.
- Given the long half-life for nivolumab and the known risk of late presenting adverse events, patients enrolled and treated on study will be followed for AEs for 180 days after the last dose of nivolumab.
- Patients will stay on study for 5 years after the last patient has been enrolled or until disease progression, whichever occurs first.

8 STUDY ENDPOINTS

8.1 Primary Endpoint

- To determine the safety of NY-ESO-1 vaccination (Anti-DEC-205-NY-ESO-1 fusion protein (CDX-1401)/poly ICLC) given in combination with decitabine and nivolumab.
  - This is a modified 3+3 design with a 12 patient expansion cohort at the maximum tolerated dose (MTD) or the maximum administered dose (MAD). We expect 18 patients to be enrolled (all at Dose Level +1(DL1)), given experience with these treatments in other studies. In DL1, decitabine will be given at 20 mg/m^2/day,

intravenously, over 1 hour on days 1-5 followed by 23 days without decitabine. If required, dose de-escalation of decitabine to 15 mg/m^2 is provided for during the safety portion of the study.

- The DLT window will begin on day -14 of cycle 1 and end on day 1 of cycle 2. The first cohort will enroll 3 patients and the DLT window for these 3 patients will end when the last patient in this group has reached cycle 2 day 1 of therapy. A second group of 3 patients will then be enrolled and treated.

All AEs and DLTs will be collected and used for descriptive characteristics for the purposes of the study.

8.2 Secondary Endpoint(s)

- To evaluate the induction of NY-ESO-1 specific cellular and humoral immunity by determination of NY-ESO-1 specific antibody, and NY-ESO-1 specific T-cell responses following standard treatment with decitabine in conjunction with immune sensitization with CDX-1401/poly-ICLC and nivolumab.
    - To evaluate the Immune cell profile in the peripheral blood and bone marrow following combination therapy using mass cytometry
    - To determine the impact of combination treatment on peripheral blood and bone marrow cells from patients treated in this manner on NY-ESO-1 target gene expression, NY-ESO-1 protein expression, NY-ESO-1 promoter methylation, and global DNA methylation.

8.3 Exploratory Endpoints

- To record the response rate (Complete Response (CR), Partial Response (PR) and Hematological Improvement (HI)) in MDS or low blast count AML patients treated with the combination in order to provide descriptive characteristics.
    - This will be assessed using results of blood counts on day 1 of each cycle.
    - A formal assessment of response will be performed Day 1 of Cycle 5 and every 4th cycle thereafter as long as patients remain on decitabine and at end of study including results of blood counts and a bone marrow biopsy. After 2 years on study, bone marrow assessments may be done every 6 cycles rather than every 4 cycles. Retrospective response assessment will include measurement of molecular measurable residual disease at serial time points.

9 DESIGN

This is an open-label, non-randomized Phase 1 study of CDX-1401 1 mg (intracutaneous) + poly-ICLC 1.8 mg (poly-ICLC will be given subcutaneously on each day of CDX-1401) vaccination, given in conjunction with decitabine x 5 days and nivolumab 3 mg/kg every 2 weeks. In dose level 1, Decitabine is dosed at 20 mg/m^2/day for 5 days/28 day cycle (Day 1-Day 5 of each cycle).

9.1 Study Design

The primary objective of this Phase I study is to determine safety of the combinatorial regimen. The secondary objective is to assess immune and molecular epigenetic response. An exploratory

objective will be to record the response rate (including Complete Response (CR), Partial Response (PR) and Hematological Improvement (HI)) in the enrolled patients who will have a diagnosis of MDS or low blast count AML patients in order to provide descriptive characteristics.

This is a modified 3+3 design with a 12 patient expansion cohort at the maximum tolerated dose (MTD) or the maximum administered dose (MAD). We expect 18 patients to be enrolled (all at Dose Level +1), given experience with these treatments in other studies.

Three patients will be accrued at dose level 1. If 0 or 1 of the first 3 patients has a dose limiting toxicity (DLT, defined in section 10), then 3 more patients will be enrolled at the same dose. If a maximum of 1 of these six patients has a DLT, dose level 1 will be declared the maximum administered dose (MAD) and an additional 12 patients will be enrolled in an expansion cohort. Dose level +1 is considered the most likely MAD, given the low observed toxicity rates with NY-ESO-1 vaccine therapy. If the true DLT rate is 20%, there is an 85% probability of ending the trial with these 18 patients. Observed toxicity rates associated with NY-ESO-1 treatment have been below 20%. The accrual decision rules are shown in Table 4.

If either of the DLT thresholds at dose level 1 is exceeded, the same rules will be followed for dose level -1. If more than one third of patients at dose level -1 have a DLT, the study will be terminated.

Table 4 Dose De-Escalation Plan

Dose Level	Number of Subjects with a Dose-Limiting Toxicity at a Given Dose Level	Escalation Decision Rule
DL 1	2,3 out of 3	De-escalate to Dose -1. Enroll 3 patients
	0,1 out of 3	Maintain Dose Level 1. Enroll three more patients
	0,1 out of 6	Declare Dose Level 1 the maximum administered dose (MAD). Enroll expansion cohort of 12 additional patients.
	≥2 out of 6	De-escalate to Dose -1. Enroll 3 patients
DL –1	2,3 out of 3	Stop the study
	0,1 out of 3	Maintain Dose Level -1. Enroll three more patients
	0,1 out of 6	Declare Dose Level -1 the maximum tolerated dose (MTD). Enroll expansion cohort of 12 additional patients.
	≥2 out of 6	Stop the study.

Patients may elect to discontinue nivolumab and/or vaccine after Cycle 8 and remain on study receiving single agent decitabine to allow collection of the secondary and exploratory endpoints as described above.

9.2 Replacing Patients

Patients enrolled in the 3+3 part who withdraw before receiving any protocol therapy will be replaced.

In the expansion cohort, patients who come off study before the end of cycle 4 for any reason not related to toxicity (and prior to the first formal response assessment following cycle 4) will be replaced.

Patients who do not complete the study through Day 29 for reasons other than DLTs will be replaced.

10 TREATMENT

Treatments will be administered predominantly on an outpatient basis. Reported adverse events (AEs) and potential risks are described in Section 13. Appropriate dose modifications are described in Section 10.3.2. No other investigational or commercial drugs or therapies other that those described below may be administered with the intent to treat the subject for their myeloid neoplasms. Patients may receive all their usual medications.

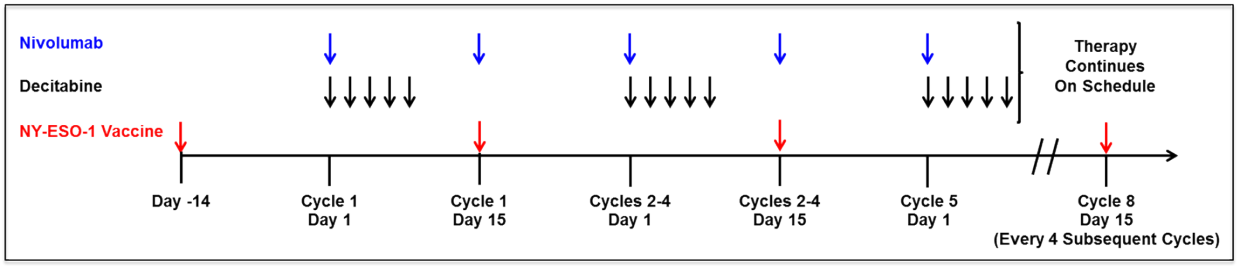
10.1 Dosing and Administration

The vaccine is comprised of CDX-1401 (1 mg) given intracutaneously with 1.8 mg of Poly-ICLC. The first dose of the vaccine is given on Day -14 and then, on Day 15 of each decitabine cycle for the first 4 cycles (total of 5 vaccines). Thereafter, patients will receive a booster vaccine on Day 1 of every 4th cycle, indefinitely.

Nivolumab is to be given at a fixed dose of 3 mg/kg every 2 weeks starting on Day 1 of Cycle 1 through cycle 4 day 15. After cycle 5 nivolumab will be given as a flat dose of 480mg every 4 weeks on day 1 of each decitabine cycle (+/-7 day window). Nivolumab administration may continue on protocol until disease progression or the patient elects to discontinue nivolumab.

Decitabine/nivolumab cycles will be given on schedule every 4 weeks unless a delay is deemed clinically necessary by the treating physician/investigator. If the patient requires a delay of more than 6 weeks, they will come off study. The study schema is depicted in **Figure 3.**

Figure 3: Study Schema



For the purposes of this study, 1 cycle = 28 days and is comprised of 5 doses of IV decitabine (days 1-5), 2 doses of nivolumab during cycles 1-4 and 1 dose of nivolumab cycles 5 and above (day 1and day 15 during cycles 1-4 or day 1 cycles 5 and above) and 1 vaccination (day 15). Protocol therapy may be given at the discretion of the treating physician within a +/-7 day window to accommodate patient's preference, clinical judgement and schedule or outside this window after discussion with the PI.

***Note*:** When nivolumab and decitabine are administered on the same day, decitabine is administered first, followed by nivolumab.

10.1.1 Vaccine (Anti DEC-205-NY-ESO-1 Fusion Protein (CDX-1401)/ Poly ICLC)

CDX-1401 and poly-ICLC will be administered on Day -14 prior to the first course of decitabine and *then* ***Day 15*** *of every cycle for the* ***first 4 cycles***. ***After Cycle 4***, CDX-1401 and poly-ICLC will

be administered on Day 1 of every 4th cycle as a booster (i.e. on day 1 of cycles 8, 12, 16, 20, 24) (see study calendar below: Section 10.1.3).

The CDX-1401 will be given as an intracutaneous injection (a mixture of subcutaneous and intradermal administration, at a dose of 1 mg); poly-ICLC will be given subcutaneously at a flat dose of 1.8 mg on each day of CDX-1401 vaccination.

Administration: Within a vaccine treatment session (consisting of one intracutaneous administration of CDX-1401 with poly-ICLC) dosing should be given within the same administration site (a 5 x 5 cm area on the extremities or the abdomen). The administration site should be free of potentially complicating dermatologic conditions, and should not be located in an area where integrity of the draining lymph node bed is potentially compromised (i.e., an extremity where a nodal resection was previously performed). For each subsequent administration session, a new administration site should be selected, with the aim of stimulating a new draining lymph node bed for each of the five administrations (Note: After the first 5 vaccinations, the vaccine may be administered in location of patient's preference). All nurses administering this vaccine will be trained to administer the doses intracutaneously prior to study implementation.

Intracutaneous injections are a combination of intradermal and subcutaneous injection. The maximum volume which can be administered intradermally is 0.1 ml and the maximum volume administered subcutaneously is considered to be 1-2 ml. Intracutaneous injections are a combination of the standard subcutaneous (many drugs) and intradermal (like a TB test) routes which are in routine use throughout the hospital. Drug will be administered using a 25G or smaller needle of ¼ to ⅝ inches in length.

- *CDX-1401* will be administered via intracutaneous injection (with approximately half of the planned dose administered by each route). Each CDX-1401 dose will be administered in a maximum volume of 1 ml, and may be split into up to 4 intracutaneous injections given within the 5 x 5 cm administration site. An appropriate needle for intracutaneous administration (25-gauge or smaller) is recommended. We have suggested that the CDX-1401 be administered in 2 injections so that no more than 0.75 ml will be given in any one spot and to avoid excess administration of drug intradermal.

- Poly-ICLC dosing will consist of one subcutaneous injection of 1.8 mg, within the 5 x 5 cm administration site. Poly-ICLC will be administered as soon as possible after the CDX-1401 injections, with the goal to administer all drugs within a one hour period.

  Note: Poly-ICLC drug product used to be labeled as 2 mg/mL but as per IB V.14 dated January 25, 2018, the labeled claim is being changed to incorporate a correction for the water content in the lyophilized components (Poly I and Poly C) and will now be listed as 1.8 mg/ml Poly-ICLC. This represents no change in the product or formulation, but simply a calculation correction. In effect, the prior 2.0 mg/mL label represented the "wet" Poly-IC concentration which is equivalent to the current 1.8 mg/mL label representing the "dry" Poly-IC concentration.

10.1.2 Nivolumab

Nivolumab will be given every two weeks (±7 days) (four weeks (two doses of nivolumab) is equivalent to one cycle of nivolumab) at a dose of 3 mg/kg/dose for the first 4 cycles of decitabine, for cycles 5 and above, nivolumab, if continued, will be given at a flat dose of 480mg every 4 weeks on day 1 of each decitabine cycle. The dosing calculations should be based on the actual body weight. If the patient's weight on the day of dosing differs by >10% from the weight used to calculate the original dose, the dose must be recalculated. All doses should be rounded to the nearest milligram if dose rounding is allowed as per institutional guidelines. There will be no dose modifications allowed.

Administration: Nivolumab is to be administered as a 30-minute (+/- 10 minutes) IV infusion, using a volumetric pump with a 0.2-1.2 micron in-line filter at the protocol-specified dose. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Reported adverse events (AEs) and potential risks are described in **Section 13**. Appropriate dose modifications are described in **Section 10.4.**

10.1.3 Decitabine

Decitabine will be given starting at dose level 1, which is the standard dose and schedule currently in use: 20 mg/m^2/day for 5 consecutive days following standard of care guidelines (50).

Decitabine will be given at 20 mg/m^2/day, intravenously, over 1 hour on days 1-5 followed by 23 days without decitabine at the discretion of the treating physician per their standard practice. Delays in dosing are allowed per standard institutional practice. Decitabine should be given Days 1-5 unless a delay is deemed necessary by the treating physician for patient safety. If required, dose de-escalation of decitabine to 15 mg/m^2 is provided for during the safety portion of the study.

Table 5 Dose Levels

Dose Level	CDX-1401/Poly-ICLC	Decitabine	Nivolumab
1	1mg/1.8mg	20mg/m2 days 1-5	3mg/kg days 1,15
-1	1mg/1.8mg	15mg/m2 days 1-5	3mg/kg days 1,15

There will be no dose modifications to the decitabine dose during the first 8 cycles of treatment. After cycle 8, dose reductions may be made at the discretion of the treating physician per their standard practice, but cycles should be given every 4 weeks unless a delay is deemed necessary by the treating physician for patient safety.

Delays in dosing up to 6 weeks are acceptable if deemed necessary for patient safety. Grade 4 neutropenia, transfusion dependence for platelets and red blood cells and the possibility of hospitalization for infections are expected toxicities of the underlying disease process and of standard treatment with decitabine.

Please see below for a detailed study calendar:

PROTOCOL TITLE: I 49217 - Phase 1 CDX-1401/ Poly-ICLC +Decitabine +Nivolumab in Patients with MDS or Low Blast Count AML

Treatment Plan: Cycle 1

Cycle 1													
Day	**-14**	**….**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**…**	**15**	**…**	**28**
CDX-1410	**X**											**X**		
Poly ICLC	**X**											**X**		
Decitabine (DAC)			**X**	**X**	**X**	**X**	**X**							
Nivolumab (NIVO)			**X**									**X**		

Treatment Plan: Cycles 2-4

Cycles 2-4														
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**…**	**15**	**…**	**28**
CDX-1410												**X**		
Poly ICLC												**X**		
Decitabine (DAC)	**X**	**X**	**X**	**X**	**X**									
Nivolumab (NIVO)	**X**											**X**		

Treatment Plan: Non-Vaccine Cycles:

Cycles 5-7, 9-11, 13-15, 17-19, 21-23, 25…													
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**…**	**15**	**…**	**28**
CDX-1410														
Poly ICLC														
Decitabine (DAC)	**X**	**X**	**X**	**X**	**X**									
Nivolumab (NIVO)	**X**													

Treatment Plan: Vaccine Booster Cycles:

Cycles 8, 12, 16, 20, 24…													
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**…**	**15**	**…**	**28**
CDX-1410	**X**													
Poly ICLC	**X**													
Decitabine (DAC)	**X**	**X**	**X**	**X**	**X**									
Nivolumab (NIVO)	**X**													

Treatment is intended for an outpatient setting. However, at the investigator's/physician's discretion, the participant may receive treatment as an inpatient, if deemed necessary.

10.2 Treatment Protocol for the Expansion Cohort

Decitabine is dosed at the MAD determined in the safety portion of the study for 5 days/28 day cycle (Day 1-Day 5 of each cycle per standard of care).

- After cycle 8, dose reductions of decitabine are permitted at the discretion of the treating investigator per the standard of care.

The vaccine is comprised of CDX-1401 (1 mg) given intracutaneously with 1.8 mg of Poly-ICLC. The first dose of the vaccine is given on Day -14 and then, on Day 15 of each decitabine cycle for

the first 4 cycles (total of 5 vaccines). Thereafter, patients will receive a booster vaccine on Day 1 of every 4th cycle, indefinitely.

Nivolumab is to be given at a fixed dose of 3 mg/kg every 2 weeks starting on Day 1 of Cycle 1. For cycles 5 and above, nivolumab is given at a fixed dose of 480mg every 4 weeks on day 1 of every cycle and may continue on protocol until disease progression or the patient elects to discontinue nivolumab.

Decitabine/nivolumab cycles will be given on schedule every 4 weeks unless a delay is deemed clinically necessary by the treating physician/investigator. If the patient requires a delay of more than 6 weeks, they will come off study.

10.3 Definition of Dose-Limiting Toxicity

Dose limiting toxicities (DLTs) are defined as any non-hematologic grade 4/5 toxicities that are definitely, probably, or possibly related to the administration of the investigational agent(s) (see Appendix H for organ specific auto-immune grading of toxicity).

All AEs will be graded according to the NCI-CTCAE scale Version 4.0.

Hematological toxicities are expected in patients with MDS undergoing therapy with decitabine and will not be considered dose limiting. Hematological toxicities will not be deemed dose limiting, in agreement with other studies in patients with MDS and AML.

The initial DLT period will be defined as 28 days after the first dose of decitabine. Given that toxicities related to checkpoint inhibitors may not be immediately manifested, after the first 3 patients have been enrolled, accrual to the expansion cohort will be delayed to monitor for late developing toxicities until all patients in the first 3 patient cohort have been followed until cycle 4 day 29 of decitabine.

Patients will be monitored throughout the study and according to the schedule of procedures and observations. Any auto-immune related events which occur between days 29 and the end of study may be sufficient to interrupt the nivolumab therapy if they are grade 4 or 5 as described below. Patients may be withdrawn from study even if DLT is due to decitabine alone.

Safety monitoring will include careful assessment and appropriate reporting of adverse events, as well as the construction and implementation of a data and safety-monitoring plan (Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events. As this is a phase I study, all AEs will be reviewed by the Early Phase Clinical Trials committee at RPCI on a weekly basis.

Management and dose modifications associated with the above AEs are outlined in Section 10.3 and Appendix H.

10.4 Dose Modifications and Treatment Delays

10.4.1 Vaccine

There will be no dose modifications to the doses of CDX-1401 or poly ICLC.

10.4.2 Decitabine

If a dose limiting toxicity is observed with combination therapy, decitabine may be dose reduced to 15mg/m2 per the safety lead in. Following the establishment of our MAD, there will be no dose reductions of decitabine in the first 8 cycles of therapy. After Cycle 8, in patients with <5% bone marrow blasts, dose reductions of decitabine are at the discretion of the investigator per the following table. Dose reductions will be recorded for informational purposes only.

Table 6 Acceptable Dose Reductions of Decitabine after Cycle 8

SOC Dose Reduction Schedule	Decitabine
1	20 mg/m^2/day for 5 days
25% dose reduction	15 mg/m^2/day for 5 days
50% dose reduction	10 mg/m^2/day for 5 days

10.4.3 Nivolumab

In the event that a patient experiences a Grade 4 treatment related toxicity due to nivolumab, myocarditis of any grade or intolerable Grade 2 or 3 toxicity, felt to be associated with Nivolumab alone, despite optimal supportive care, treatment with Nivolumab should be permanently discontinued. Refer to **Table 7** for recommended nivolumab dose modifications. If toxicities have resolved to <grade 1, nivolumab may be reintroduced following a period of holding.

Table 7 Nivolumab Dose Modifications and Dosing Delays

Adverse Reaction	Severity	Dose Modification
Myocarditis	Any grade	Permanently discontinue
Colitis	Grade 2 diarrhea or colitis	Withhold dose [a]
	Grade 3 diarrhea or colitis:	
	• Single-agent Nivolumab	Permanently discontinue
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose [a]
	Grade 3 pneumonitis	Permanently discontinue
Hepatitis	Aspartate aminotransferase (AST)/or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal or total bilirubin more than 1.5 and up to 3 times the upper limit of normal	Withhold dose [a]
	AST or ALT more than 5 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal	Permanently discontinue
Hypophysitis	Grade 2 or Grade 3 hypophysitis	Withhold dose [a]
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose [a]

Adverse Reaction	Severity	Dose Modification
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose [a]
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 2 times the upper limit of normal	Withhold dose [a]
	Serum creatinine more than 2 times the upper limit of normal	Permanently discontinue
Rash	Grade 3 rash	Withhold dose [a]
	Grade 4 rash	Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose [a]
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reactions:	
	• First occurrence	Withhold dose [a]
	• Recurrence of same Grade 3 adverse reactions	Permanently discontinue
	• Life threatening or Grade 4 adverse reaction	Permanently discontinue
	• Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	• Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

[a]: withhold dose and resume nivolumab with the next cycle if resolution of toxicity to ≤ Grade 1.

10.4.3.1 Guidelines on Myocarditis attributed to Nivolumab

For all cardiac safety marker elevations (troponin, CK-MB, BNP), whether in isolation or in combination, nivolumab will be held until investigations can exclude nivolumab. Consult cardiology immediately. If there is high clinical suspicion for nivolumab-induced myocarditis, high-dose steroids (1 gram IV methylprednisolone or equivalent) must be started during hospitalization regardless of availability of cardiac MRI or echocardiogram findings.

If patient is asymptomatic/at baseline but there is new isolated BNP elevation, obtain echocardiogram immediately. Daily clinic assessment including cardiac biomarkers should be performed if patient's symptoms are unchanged from baseline, echocardiogram normal or baseline, additional safety markers and vital signs remain normal. If patient has new symptoms e.g. weakness, fatigue, dyspnea, edema, etc. regardless of severity accompanied by isolated BNP elevation, cardiac MRI must be obtained as soon as possible regardless of echocardiogram findings. Hospital admission for cardiac monitoring must be considered along with institution of supportive medications.

If patient is asymptomatic/at baseline with normal renal function but troponin rises to greater than 0.10, investigate for the presence of acute pulmonary embolism and acute coronary syndrome in addition to guidelines above.

Hold treatment if patient is asymptomatic but new persistent ECG changes noted on triplicate readings along with normal troponin, CK-MB, BNP and echocardiogram. Consult cardiology. Repeat ECG and labs no earlier than 12 hours later. If ECG changes are transient, may continue treatment.

For documented echocardiographic changes regardless of cardiac safety marker levels, cardiac MRI must be obtained. Hold study treatment. If treatment-induced myocarditis is suspected, high-dose steroids must be instituted as detailed above.

10.5 General Concomitant Medication and Supportive Care

Subjects will receive standard pre-treatment with anti-emetics prior to decitabine administration. Subjects may be treated for breakthrough nausea and vomiting with appropriate anti-emetics.

The use of all standard supportive medication is permitted, although concurrent treatment with immunosuppressive or immunomodulatory agents is strongly discouraged. Concomitant systemic corticosteroids are to be avoided if at all possible. If used, doses of steroids should be the minimum necessary for appropriate clinical management. If clinically necessary, topical or systemic non-steroidal anti-inflammatory or antihistamines may be used as alternatives.

Subjects should not be receiving concomitant long-term corticosteroids at a dose greater than 15 mg of prednisone equivalents. The use of corticosteroids for management of nausea, osteoarthritis gout, or other symptoms at doses less than 15 mg of prednisone equivalents is permitted.

The Investigator may, at his/her discretion, arrange for a patient to have an unscheduled visit, especially in the case of AEs that require follow-up. If a patient is experiencing an AE considered by the Investigator to be possibly related to the study drug, an unscheduled visit should be performed; the unscheduled visit pages for the eCRF must be completed.

10.6 Duration of Treatment

Participants may remain on study and continue to receive treatment in the absence of disease progression, unacceptable toxicity or withdrawal from study, intercurrent illness that prevents further administration of treatment, participant demonstrates an inability/refusal to comply with study therapy or participant withdraws from study. Patients who remain on study (receiving combination therapy, decitabine/nivolumab, or single agent nivolumab) will continue to have response assessment every 4 cycles for the first 2 years and every 6 cycles thereafter. Patients can withdraw from study at any time. Patients who proceed to allogeneic bone marrow transplant or who require a change of therapy for disease progression will come off study.

10.7 Compliance

All study related medications will be provided either subcutaneously, intracutaneously (combination of subcutaneously and intradermally) or intravenously. Patients will come for lab checks for routine monitoring and to obtain study blood work. Blood work may be done on a

± 2 day window from the day indicated on the study calendar in order to minimize subject noncompliance and with the recognition that there are sometimes commitments which cannot be re-scheduled. Patients must be seen on day 1 of each course of therapy and undergo a complete physical examination and review of toxicity.

11 PROCEDURES INVOLVED

The study-specific assessments are detailed in this section and outlined in **Appendix J (**Schedule of Procedures and Observations). Baseline and/or Screening assessments must be performed within 14 days prior to the first dose of investigational product. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All on-study visit procedures are allowed **a window of ± 2 days** unless otherwise noted.

11.1 Participant Randomization and Registration

Eligibility of each participant will be established prior to enrollment.

Informed consent ***MUST*** be completed prior to receiving any study related procedures.

11.2 Baseline Evaluations

Confirmation of Eligibility: The following will be performed *within 4 weeks* prior to first dose of CDX-1401/poly ICLC (unless otherwise indicated):

- Medical history with pre-existing conditions
- Physical examination
- Vital signs (i.e., temperature, heart rate, respiratory rate, O_2 saturation, blood pressure), body weight and, height. Height collected at baseline only
- Hematology: CBC with manual differential
- Chemistry: CMP. In addition: LDH, uric acid, amylase and, lipase
- Pregnancy test urine, in females of childbearing potential (within 1 week prior to first dose of study drug)
- ECOG Performance Status
- HLA Typing: May use historical sample if available (patients who do not require HLA typing for determination of transplant eligibility will have HLA typing sent for study purposes)
- IPSS/ IPSSR (Refer to Appendix E and Appendix F for calculation instructions)
- Testing for HIV I/II Ab, HBsAg, HCV Ab+/- PCR (should be done only in patients for whom there is a concern for prior infection with one of these viral pathogens. Testing is NOT required if there is no history of infection)
- Bone Marrow Aspirate and Biopsy (with Flow Cytometry, Conventional Cytogenetics +/- FISH as appropriate).In addition:
    - Study Bone marrow samples for T-cell and methylation and gene expression studies (Section 11.11.2)

- Correlative blood sampling
- Endocrine Function Evaluation: TSH, blood glucose testing
- Concomitant Medications (List any ongoing medications with an onset within 1 week of first dose of study drug.).

The following will be performed *within 4 weeks* prior to first dose of study drug:

- Cardiac safety markers: troponin-I, BNP, CK-MB
- Electrocardiogram (ECG)
- Echocardiogram
- Urinalysis

11.3 Evaluations Performed on Day -14

- Physical examination including vital signs
- Hematology: CBC with manual differential
- Chemistry: CMP. In addition: LDH, uric acid, amylase and, lipase
- ECOG Performance Status
- Correlative blood sampling (see Section 11.11.1)
- CDX-1401/ poly-ICLC administration
- Concomitant medications
- Adverse events

11.4 Evaluations Performed on Day 1 of each Cycle

The following evaluations will be performed prior to CDX-1401/poly ICLC dosing or infusion of decitabine on Day 1 of each cycle or prior to premedication, if administered (may be performed up to 3 days prior to day of infusion), unless otherwise indicated:

- Physical examination
- Vital signs (i.e., temperature, heart rate, respiratory rate, oxygen saturation, blood pressure, body weight)
- Hematology: CBC with manual differential (Once per week of each cycle during cycles 1-4, from cycles 5 onward on day 1 and as clinically indicated)
- Hematological Improvement (HI)) in MDS or low blast count AML patients treated with the combination in order to provide descriptive characteristics.
    - This will be assessed using results of blood counts on day 1 of each cycle.
- Chemistry: CMP, LDH, uric acid, amylase and, lipase (Once per week each cycle during cycles 1-4, from cycles 5 onward on day 1 and as clinically indicated)
- ECOG performance status

- Correlative blood sampling prior to study drug dosing Once per week each cycle during Cycles 1-4; from Cycle 5 onward once every 2 weeks (see Section 11.11.1)
- Decitabine administration: Day 1-Day 5 of each cycle (per standard of care for patient safety)
- Nivolumab administration: Day 1 and Day 15 of each cycle (+/-7 days)
- Concomitant Medications
- Adverse events

11.5 Evaluations Performed on Day 15 of each Cycle

- Vital signs
- Hematology: CBC with manual differential (see Section 11.4)
- Chemistry: CMP, LDH, uric acid, amylase and, lipase (see Section 11.4)
- CDX-1401/poly-ICLC administration (Day 15 of every cycle for the ***first 4 cycles***: thereafter, to be given on ***Day 1 of every 4th cycle*** as a booster (i.e. on Day 1 of cycles 8, 12, 16, 20, 24).
- Nivolumab administration (Day 15 for ***first 4 cycles***: thereafter, to be given on ***Day 1 of every 4th cycle)***
- Adverse events

11.6 Evaluations Performed Specifically at End of Cycle 1

- Endocrine Function Evaluation: TSH and blood glucose
- Bone Marrow Aspirate and Biopsy (**Note:** At the end of Cycle 1, if a bone marrow aspirate is not able to be done, a bone marrow biopsy may be performed instead). In Addition:
    - Study Bone marrow samples for T-cell and methylation and gene expression studies (Section 11.11.2)
- The following cardiac safety tests will be performed at the end of Cycle 1 and as clinically indicated:
    - Cardiac Safety Markers: Troponin-I, CK-MB, BNP
    - ECG
- Adverse events
- Urinalysis

11.7 Evaluations Performed on Cycle 5 Day 1 and every 4th Cycle thereafter

The following evaluations will be performed on or after day 28 of every 4th cycle of decitabine, and prior to initiation of any further therapy. In general samples and bone marrow should be done on day 29 (i.e., day 1 of a cycle) at cycles 5, 9, 13, 17, etc… of decitabine, per standard of care:

- Physical examination, including vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure) and body weight
- Hematology: CBC with manual differential
- Chemistry: CMP, LDH, uric acid, amylase, lipase
- Urinalysis
- Correlative blood sampling prior to study drug dosing: once every 2 weeks (see Section 11.11.1)
- IPSS/ IPSSR (Refer to Appendix E and Appendix F for calculation instructions)
- Concomitant medication
- Adverse events
- Bone Marrow Aspirate and Biopsy (with flow cytometry, conventional cytogenetics and FISH studies as deemed appropriate by the treating physician). In addition:
    - Study Bone marrow samples for T-cell and methylation and gene expression studies (Section 11.11.2)
- Response assessment per modified International Working Group criteria for MDS (refer to Appendix D, Appendix E and Appendix F) and TTT

11.8 Evaluations Performed at End of Treatment

The following evaluations will be performed ± 4 days from day 29 of the last cycle of decitabine, and prior to initiation of any further therapy:

- Physical examination and vital signs
- Hematology: CBC with manual differential
- Chemistry: CMP
- ECOG Performance Status
- IPSS/ IPSSR (Refer to Appendix E and Appendix F for calculation instructions)
- Bone marrow aspirate and biopsy (with flow cytometry, conventional cytogenetics and FISH studies as deemed appropriate by the treating physician). In addition:
    - Bone marrow samples for T-cell and methylation and gene expression studies (Section 11.11.2)
- Blood sample for immune correlates (Section 11.11.1)
- Concomitant medications
- Adverse events
- Response assessment per modified International Working Group criteria for MDS (refer to Appendix D, Appendix E and Appendix F) and TTT

11.9 Post-Treatment Follow-Up Evaluations

Follow-up safety evaluations will occur 30 days (± 3 days), 60 days (± 3 days), 90 days (± 3 days), and 180 days (± 3 days) after last dose of study drug or until resolution of any drug-related toxicity (telephone contact is acceptable). Patients will be asked to report any possible auto-immune reactions (including rashes, skin changes, new symptoms of arthritis or other auto-immune phenomena) in order to capture possible late manifestations of auto-immunity.

- Concomitant medications
- Adverse events
- Survival Status: Disease progression/change in treatment

Patients remaining on study for ≥ 2 years will have a bone marrow biopsy performed every 6 months (± 2 months) per standard of care follow up.

11.10 Schedule of Procedures and Observations

The schedule of procedures and observations for this study is summarized in **Appendix J.**

11.11 Correlative Studies

11.11.1 Blood Sample Collection

Blood samples will be collected via venipuncture (green tops) for analysis of molecular markers, NY- ESO-1 cellular immune response (T-cell), (ELISPOT and ICS) and assessment of T-Regulatory cell frequency (CD4+CD25+FOXP3+ regulatory T cells) and, cell differentiation by transcription factor distribution (T-bet, GATA-3, RORγ) and, gold-top tubes will be used for analysis of antibody response (NY-ESO-l-ELISA).

- Blood will be collected at the following time points:
    - Baseline:
        - 4, 10 mL green-top (sodium heparin) tubes (Dr. Griffith's lab)
        - 2, 10 mL green-top (sodium heparin) tubes (Immune Analysis Facility)
        - 1, 3.5 mL gold-top tube (Immune Analysis Facility)
    - Day -14 (prior to Cycle 1 Day 1):
        - 4, 10 mL green-top (sodium heparin) tubes (Dr. Griffith's lab)
        - 2, 10 mL green-top (sodium heparin) tubes (Immune Analysis Facility)
        - 1, 3.5 mL gold-top tube (Immune Analysis Facility)
    - Cycles 1-4 (once weekly):
        - 4, 10 mL green-top (sodium heparin) tubes (Dr. Griffith's lab)
        - 2, 10 mL green-top (sodium heparin) tubes (Immune Analysis Facility)
    - Cycle 5 and onward until end of treatment (Day 1 and Day 15) and, end of treatment:
        - 4, 10 mL green-top (sodium heparin) tubes (Dr. Griffith's lab)
        - 2, 10 mL green-top (sodium heparin) tubes (Immune Analysis Facility)
        - 1, 3.5 mL gold-top tube (Immune Analysis Facility)

Note: If it is determined that there is an inadequate cell number for cryopreservation and immunomonitoring at any visit, sample acquisition may be repeated at the next scheduled blood draw.

11.11.2 Bone Marrow Sample Collection

Study Bone marrow samples for T-cell and methylation and gene expression studies: 4, 10 mL green-tops tubes (sodium heparin) to be obtained each time a bone marrow assessment is to be done.

- Bone marrow samples will be collected at the following time points:
    - Baseline
    - End of Cycle 1 (**Note:** At the end of Cycle 1, if a bone marrow aspirate is not able to be done, a bone marrow biopsy may be performed instead)

- Day 1 Cycle 5 and, Day 1 of every 4th cycle thereafter (+/- 14 day window acceptable)
- End of treatment
- If bone marrow is unable to be collected at noted time point and clinically appropriate, a bone marrow samples should be performed next cycle to document disease status.
- If a bone marrow is unable to be collected due to dry tap, collect 4 additional, 10 mL green-tops tubes (sodium heparin) of peripheral blood

Blood and Bone Marrow Processing

Samples (blood and/or bone marrow) will be processed at each site (**Appendix G**). The cryovials are to be labeled with the clinical study number and patient study ID, collection date/study cycle and day and "Blood" or "Bone marrow."

The cryovials will immediately be frozen in liquid nitrogen and stored until requested for batch mailing. Samples are to be batch shipped frozen, on dry ice to:

Roswell Park Cancer Institute
Dr. Griffiths Laboratory
Attn: Pragya Srivastava, I 49217 Samples
CGP L5-201
Elm and Carlton Streets
Buffalo, NY 14263
Telephone #: (716) 845-1724 (lab) or,
(716) 430-1152 (cell)
Pragya.Srivastava@RoswellPark.org

For Network Sites: Follow directions above for sample collection and processing. The cryogenic tubes are to be labeled with the clinical study number and patient study ID, collection date/study cycle and day and, "Blood" or "Bone marrow". The processed samples will immediately be frozen in liquid nitrogen and stored until requested for batch mailing. Samples are to be batch shipped frozen, on dry ice.

Frozen samples will be shipped via Fed Express Overnight on dry ice with delivery on Mon-Fri. NO SATURDAY DELIVERY. Do not ship on a Friday or the day before a holiday.

Note: All investigator or analyzing research laboratories housing research samples need to maintain current Temperature Logs and study-specific Sample Tracking and Shipping Logs. The Principal Investigator/Laboratory Manager must ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens. This is required for both observational and interventional clinical studies collecting clinical samples

Cellular and/or humoral immune response assays (see below) will be performed by the RPCI Immune Analysis Facility under the direction of Dr. Junko Matsuzaki:

Roswell Park Cancer Institute
Immune Analysis Facility Shared Resource

Cancer Cell Center, 4th Floor, Room 416
Elm and Carlton Streets
Buffalo, NY 14263
Telephone #: (716) 845-8459

Junko.Matsuzaki@RoswellPark.org

11.11.3 Molecular (Epigenetic) Markers of Response

Assays of samples to determine if circulating cells demonstrate the expected changes in global and gene specific (NY-ESO-1) methylation, gene expression (NY-ESO-1) and protein expression (NY-ESO-1) responses will be performed in the Griffiths Laboratory at the RPCI, Buffalo, NY. Assessment of molecular response, by error corrected sequencing, to protocol therapy will be sent out to Dr. Hourigan's Laboratory at the National Institutes of Health.

These assays are in routine use in my laboratory (see Figure 1) and we anticipate no difficulties performing them. Myeloid cells will be enriched from whole blood using CD11b MicroBeads and the MACS® Column separation method (Miltenyi Biotec, Bergisch-Gladbach, Germany). DNA, RNA and protein will be extracted using QIAamp DNA/RNA/Protein Mini and QIAamp DNA Blood Maxi kits (Qiagen, Valencia, CA). Given that some patients with MDS have very low numbers of circulating cells, isolation of the myeloid compartment may limit sample quality, and thus if separation proves unsuccessful, we will isolate DNA, RNA and protein from whole blood instead as this method has also been validated in MDS patients receiving HMA therapy (51). We have successfully collected informative samples from other MDS patients in this manner without difficulty. Any samples that are not informative will be censored. At each time point NY-ESO-1 promoter methylation (by bisulfite pyrosequencing) and NY-ESO-1 mRNA (by RT-PCR) will be determined. Assessment of LINE-1 methylation (also by bisulfite pyrosequencing) will be done as a marker for changes in global methylation over the course of each cycle (4, 52). One sample per week will be assayed for NY-ESO-1 protein expression by Western Blot (maximum 16 per patient). These analyses will allow us to demonstrate changes in NY-ESO-1 over the course of the treatment cycle and correlate them with the immunological parameters described below

11.11.4 Immunological Markers of Response

Assays to determine whether vaccination with CDX-1401/poly ICLC in series with decitabine and nivolumab can induce NY-ESO-1 specific cellular and/or humoral immune responses will be performed by the Immune Analysis Facility. MDS is characterized by bone marrow hypercellularity in association with peripheral blood cytopenias, increased rates of infection and autoimmune phenomena (53-55). Despite overt cytopenias and the possibility that in MDS the immune system does not function normally, we and other authors have successfully induced antigen specific T-cells following neo-antigen vaccination in patients with MDS and endogenous humoral immunity has also been shown [(56, 57) and Srivastava P et al. Blood 2016;128: 4326]. Therefore, we anticipate that induction of NY-ESO-1-specific immune responses is feasible. We are eager to test if the addition of nivolumab to our prior backbone will result in substantial enhancement of such responses. Furthermore, since induction of interferon-gamma (IFNγ) producing CD4+ and CD8+ T-cells are associated with improved clinical outcome in ovarian cancer patients expressing NY-ESO-1, documentation of a sustained immunological response in

MDS is of significant potential clinical interest (58, 59). Two major potential mechanisms that could account for a failure to induce NY-ESO-1 specific T- and B-cell responses include APC dysfunction and the activity of Tregs.

11.11.5 Humoral Immunity

We will test patients treated on the study for the production of NY-ESO-1 specific antibodies. Since documentation of a humoral immune response is associated with the activity of cancer vaccines in solid tumors such a response would be of interest (60). Induction of NY-ESO-1 specific antibody will be tested serially at baseline, at the end of cycle 4 and every 4^{th}-8^{th} cycle of decitabine therapy. An ELISA assay will be used to measure anti-NY-ESO-1 antibody titers (61). Comparison of antibody titers over the course of therapy will allow us to determine the humoral immunogenicity of this combination.

Specific antibody against NY-ESO-1 will be measured by ELISA [(62) for methodology]. Assays will be performed by the Roswell Park Cancer Center Immune Analysis Facility.

11.11.6 Cellular Immunity

The ability of the vaccine alone and in combination with decitabine and nivolumab to induce NY-ESO-1 specific, IFNγ secreting CD4+ and CD8+ T-cells will be measured. Samples will be obtained at baseline, and serially as described above. NY-ESO1 specific T-cell responses will be assessed using an in vitro T cell pre-sensitization, a method for the amplification of broadly HLA reactive NY-ESO-1-specific CD8+ and CD4+ T cells (51). Positive control stimulation with CEFT peptide (cytomegalovirus, Epstein-Barr virus, flu viruses (collectively) and tetanus toxoid (T) epitopes) is set up in parallel. Ten to 14 days after pre-sensitization, the frequency and the response of NY-ESO-1 specific cells will be analyzed by intracellular cytokine staining and ELISPOT assays for IFNγ as previously described (63). Comparison of the frequency of NY-ESO-1-specific T cells at baseline with samples derived serially will allow us to determine the immunogenicity of our combination. In addition to the peripheral blood studies described here, pre-treatment and off study bone marrow samples will be assessed for the presence of NY-ESO-1 specific T-cells as above and analyzed by flow cytometry for frequency of CD4+, CD8+, FOXP3+ and CD19+ cells.

11.11.7 Dendritic Cell Function

In the event that we do not observe antigen specific immune responses, this could reflect APC dysfunction related either to the underlying malignancy, or to treatment with decitabine. The function of APCs in MDS has not been tested, thus we will determine whether cultured APCs from our enrolled MDS patients are able to effectively process and present antigen in order to activate T-cells. Exposure to decitabine has been previously shown to enhance the development and maturation of APCs in solid tumor models (64), as well as to enhance immune recognition in other hematological malignancies (65). We will examine APC function at baseline and following 2 and 4 cycles of decitabine treatment (3 time points). For these assays, blood samples will be obtained and cultured under conditions known to induce APC differentiation (66, 67). The ability of these cells to activate NY-ESO-1 specific T-cells derived from either autologous peripheral blood mononuclear cells or from ovarian cancer patients with NY-ESO-1 expressing tumors, (depending upon the HLA type of the patient) will be determined by the ELISPOT technique for IFNγ, as above. We will also assess the ability of these cells to induce an allo-reactive T-cell response from

healthy donor T-cells. These assays will test the function of APCs in MDS patients and determine if exposure to decitabine has an effect upon this function.

The induction of antitumor T-cell responses associated with IFNγ production are believed to be critical to the effects of cancer vaccination in solid tumors, however such responses are limited by the action of immunosuppressive Tregs which allow escape by malignant cells (59, 60, 68). Recently Tregs have been demonstrated to be complex, differentiating and migrating in response to signals from the immune system (60). Specific subsets of Tregs have been demonstrated to have differential suppressive effects upon anti-tumor immune responsiveness (60, 69). One study in MDS and AML patients treated with azacitidine following BMT suggests that HMAs alter Treg function by promoting graft versus leukemia effects over graft versus host effects, while another has demonstrated enhanced immuno-suppressive effects (49, 68). In order to determine if MDS patients undergoing therapy with CDX-1401/poly ICLC decitabine and nivolumab demonstrate changes in Treg differentiation favoring anti-tumor immune responsiveness over immune suppression, we will analyze Tregs sampled serially for changes in the expression of markers (including CD127, CD45RA, CXCR3 and Helios) associated with Treg biological function using flow cytometry (56, 59, 70, 71). Significant changes in Treg subsets with therapy would suggest that decitabine can alter the immune milieu in patients with MDS.

The methods to analyze the T cell response to cancer antigens used in this study are well established. However, as T cell biology and immune regulation are very active fields of discovery, the opportunity exists to refine and extend the analysis of the T cell response. Therefore, although most of the blood drawn for the analysis of the immune response will be used for the assays listed in this section, a small part may be used to explore other aspects of the T cell response using novel techniques such as time of flight cytometry. This work may also involve establishing T cell lines and clones in culture, and collaborations with investigators outside of Roswell Park Cancer Institute. As these exploratory approaches, by definition, have not yet been validated, the results will not be endpoints in the evaluation of the current study.

11.11.8 Additional Exploration of the T cell Response

Specimens will be stored for future use/analysis: The subjects enrolled at RPCI will have signed a separate consent for the taking, storage, and future research upon these samples under protocol CIC 98-05.

12 WITHDRAWAL OF SUBJECTS

Participants may remain on study and continue to receive treatment in the absence of disease progression, unacceptable toxicity or withdrawal from study, intercurrent illness that prevents further administration of treatment, participant demonstrates an inability/refusal to comply with treatment or, participant withdraws from study.

12.1 Treatment Discontinuation

Upon treatment discontinuation all end of treatment evaluations and tests will be conducted. All participants who discontinue due to an AE must be followed until the event resolves or stabilizes. Appropriate medical care should be provided until signs and symptoms have abated, stabilized, or until abnormal laboratory findings have returned to acceptable or pre-study limits. The final status of the AE will be reported in the participant's medical records and the appropriate eCRF. Patients

with dose limiting toxicities requiring drug discontinuation will be removed from the study and will not be replaced.

Reasons for treatment discontinuation should be classified as follows:

- Death
- Progressive disease
- Toxicity; treatment related or unrelated
- Investigator judgment
    - The Investigator may discontinue a participant if, in his/her judgment, it is in the best interest of the participant to do so.
- Noncompliance
- Participant voluntary withdrawal
    - A participant may withdraw from the study at any time, for any reason. If a participant discontinues treatment, an attempt should be made to obtain information regarding the reason for withdrawal.
- Sponsor Investigator's decision.

13 RISKS TO SUBJECTS

13.1 Vaccine (Anti DEC-205-NY-ESO-1 Fusion Protein (CDX-1401)/ Poly ICLC)

Expected toxicities with CDX-1401/poly ICLC include injection site reactions, including rash, erythema, pruritus, pain, induration and swelling. Additional reported treatment-related toxicities with this agent have been mild to moderate in severity, and include fatigue (24%), decreased appetite (14%), nausea (10%), arthralgia (10%), headache (10%) and pruritus (10%).

13.2 Nivolumab

In ongoing studies that combine nivolumab and HMAs in patients with myeloid malignancy (45, 46), the following adverse events have been reported:

- In 39 patients with MDS either previously untreated or relapsed after HMA failure (45):
    - 45%: constipation and maculopapular rash
    - 36%: nasal congestion
    - 27%: arthralgia, cough, stomach pain
    - 18%: diarrhea, edema, fatigue, hyperkalemia, insomnia
    - 9%: anorexia, dyspnea, GERD, hyperglycemia, hyponatremia, hypotension, mucositis, nausea, pneumonitis, weight loss

The most commonly reported $\geq$ Grade 3 adverse events in the combination arm (n=11) were pulmonary infections (seen in 18% of patients), followed by intracranial hemorrhage, hyperglycemia, fever and elevated LFTs (in 9% each).

- In 51 patients with relapsed or refractory AML treated to date and analyzed after a total of 3 courses of therapy (46), notable toxicities reported included:

- Grade 3/4 and Grade 2 immune mediated toxicities in 7 (14%) and 6 (12%) pts.
- Pulmonary toxicity was prominent in this population with 8 episodes of pneumonitis
- Other toxicities included 2 reports of nephritis, 2 reports of transaminitis, and 1 skin rash.
- There was one death on study deemed related to grade 4 pneumonitis/epiglottitis
- Four patients were post-SCT and one had a grade 3 flare of GVHD of the skin and gut

Toxicities were reported to respond rapidly to steroids. Patients were successfully re-treated with nivolumab after resolution of toxicity. Time to onset of toxicities ranged from 4 days to 3.5 months.

Refer to **Appendix I** for reported adverse drug reactions for nivolumab monotherapy.

Note: All adverse drug reactions for nivolumab monotherapy are also adverse drug reactions for nivolumab in combination with ipilimumab and other agents. A description of adverse drug reactions nature and frequency observed with nivolumab in combination with ipilimumab can be found in the nivolumab Investigator Brochure (v16, Table 5.6.1-2)

13.2.1 Management of Immune-Related Adverse Events

Nivolumab is approved in multiple solid tumor indications as well as for Hodgkin lymphoma based on its favorable benefit/risk assessment. In hematological malignancies including multiple myeloma, nivolumab monotherapy was generally well tolerated and toxicity profile was similar to that observed in solid tumors. Nivolumab has the potential for clinically relevant immune-related AEs potentially caused by an inflammatory mechanism. These include pulmonary toxicity, hepatotoxicity, diarrhea/colitis, endocrinopathies, and nephrotoxicity.

To date, these immune-related AEs have been manageable with frequent monitoring, prompt diagnosis, and initiation of corticosteroids, dose interruption, and adequate supportive care.

Refer to **Appendix H** for algorithm guidelines for the management of immune-related adverse events.

13.3 Decitabine

Autoimmune reaction (antiplatelet antibodies, erythema nodosum), decreased hemoglobin, decreased leukocytes (total WBC), decreased neutrophils/granulocytes (ANC/AGC), decreased platelets, febrile neutropenia with or without infection, fatigue (lethargy, malaise, asthenia), alopecia, diarrhea, peritonitis, nausea, vomiting, anorexia, stomatitis /pharyngitis (oral/ pharyngeal, mucositis), increase bilirubin, increased SGOT (AST) (serum glutamic oxaloacetic transaminase), increased SGPT (ALT) (serum glutamic pyruvic transaminase), depressed level of consciousness, abdominal pain or cramping.

The following have been reported on decitabine trials with the relationship to decitabine still undetermined: Allergy, GVHD, atrial fibrillation, thrombosis, phlebitis, cardiac ischemia, cardiac arrest (one case), face edema, hypotension, cardiac failure/arrest (MI), congestive heart failure, veno-occlusive disease, ascites, cardiac decompensation, fever, chills, drug fever, weight loss, skin rash, itching, taste disturbance, constipation, cholecystitis, perianal abscess, ileus, hematuria, liver failure, increased alkaline phosphatase, reactivation of herpes simplex, hyponatremia, neuropathy,

depression, dizziness, headache, lightheadedness, restlessness, sleep disorder, seizures, hemiparesis, somnolence, myalgia, bone pain, dyspnea, hiccups, pulmonary edema, ARDS, cough, increased creatinine, dysuria, renal failure, bone marrow aplasia, infectious complication (including sepsis, infection cellulites, pneumonia), GI bleed, cerebral hemorrhage, cerebral ischemia, lung hemorrhage, differentiation syndrome, infection with normal absolute neutrophil count.

14 POTENTIAL BENEFITS TO SUBJECTS

Based on the results of pre-clinical and clinical studies, the addition of nivolumab to standard NY-ESO-1 vaccine/decitabine may improve T cell immune response to NY-ESO-1vaccination in MDS/AML patients.

15 DATA AND SPECIMEN BANKING

As this is a Phase 1 study, the secondary endpoints are entirely correlative and designed to determine if CDX-1401/poly ICLC in combination with nivolumab and decitabine can induce anti-NY-ESO1 specific immune responses. If these responses are observed in the absence of toxicity, the data will be used to justify a larger study to determine the efficacy of the combination in patients with MDS.

Patients will be sampled serially in this trial in order to determine the degree to which MDS patients treated with decitabine develop NY-ESO-1 promoter hypomethylation and induce NY-ESO-1 mRNA and/or protein expression in circulating myeloid cells. The induction of global and gene specific hypomethylation has been repeatedly documented in patients with MDS and AML treated with hypomethylating drugs (4, 17, 72). We and others have shown that decitabine treatment induces NY-ESO-1 as well as a variety of other CTAs in circulating blasts (Figure 1),(17, 18) and furthermore that such induction of gene expression can be immunogenic (49, 73). In our previous study combining NY-ESO-1 vaccination with decitabine in MDS patients we demonstrated induction of NY-ESO-1 mRNA in circulating CD11b myeloid cells (See Figure 1). We further showed that the cell free DNA compartment recapitulates the methylation signature in circulating cells. In this study samples will be analyzed to confirm induced expression of NY-ESO-1 mRNA in circulating CD11b selected cells. Cell free DNA will be used to assess changes in methylation status at the LINE-1 and NY-ESO-1 promoters. These data will be correlated with observations of NY-ESO-1 specific immune responses.

For subjects enrolled at the Roswell Park Cancer Institute, if a subject does not have enough sampled peripheral blood taken at any time point to conduct these studies, we will add to that by using samples that subject has on hand in the Roswell Park Hematologic Procurement Facility.

Subjects enrolled at RPCI have signed a separate consent for the taking, storage, and future research upon these samples under protocol CIC 98-05.

16 MEASUREMENT OF EFFECT

Objective responses will be recorded and graded at the end of every 4th cycle of treatment using the modified International Working Group Criteria for MDS and AML patients as detailed in **Appendix D**, **Appendix E** and **Appendix F**. Molecular assessment of measurable residual disease (using accrued blood and/or bone marrow samples) will be assessed serially in a retrospective fashion in collaboration with Dr. Christopher Hourigan at the National Institutes of Health.

Samples will be sent de-identified to Dr. Hourigan's laboratory and results will be reviewed and analyzed by the study team and correlated with immunological response to therapy.

17 SAFETY EVALUATION

17.1 Adverse Events

An adverse event or adverse experience (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of 'unrelated', 'unlikely', 'possible', 'probable', or 'definite').

An AE is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan in other study-related documents.

17.1.1 Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be clinically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

17.1.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the CRF. However, clinically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

17.1.3 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF. If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself

should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7 mEq/L should be recorded as "hyperkalemia".

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.

17.1.4 Preexisting Medical Conditions (Baseline Conditions)

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

17.2 Grading and Relationship to Drug

The descriptions and grading scales found in the CTEP Version 4 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. CTEP Version 4 of the CTCAE is identified and located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

AEs not covered by specific terminology listed should be reported with common medical terminology, and documented according to the grading scales provided in the CTCAE Version 4.

The relationship of event to study drug will be documented by the Investigator as follows:

- **Unrelated:** The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs administered to the participant.
- **Unlikely:** The event is doubtfully related to investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible:** The event follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs.
- **Probable:** The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions or concomitant drugs.
- **Definite:** The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions or concomitant drugs; AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

17.3 Reporting Adverse Events

Routine AEs occurring between the start date of intervention until 180 days after the last intervention, or until the event has resolved, the study participant is lost to follow-up, the start of

a new treatment, or until the study investigator assesses the event(s) as stable or irreversible, will be reported. New information will be reported after it is received.

Guidelines for Routine Adverse Event Reporting for Phase 1 Studies (Regardless of Expectedness)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4
Unrelated	X	X	X	X
Unlikely	X	X	X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

17.4 Serious Adverse Events

A serious adverse event (SAE) is any adverse event (experience) that in the opinion of either the investigator or supporter results in **ANY** of the following:

- Death.
- A life-threatening adverse event (experience). Any AE that places a participant or participants, in the view of the Investigator or supporter, at immediate risk of death from the reaction as it occurred. It does NOT include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.
- Important Medical Event (IME) that, based upon medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

17.4.1 Reporting Serious Adverse Events

All new SAEs related to study procedures occurring from the date the participant signs the study consent until the start date of intervention or date of screen fail will be reported. All new SAEs occurring from the start date of intervention until 180 days after the last intervention or a new treatment is started, whichever comes first, will be reported. The RPCI SAE Source Form is to be completed with all available information, including a brief narrative describing the SAE and any other relevant information.

SAEs occurring after the 180 day follow-up period that the investigator determines to be possibly, probably or definitely related to the study intervention should be reported.

SAEs identified as an Unanticipated Problem by the Investigator must be reported. Please refer to **Section 17.7** for details on reporting Unanticipated Problems.

17.5 Investigator Reporting: Notifying the Study Supporter

All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 30 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

Follow-up safety evaluations will occur 30 days (± 3 days), 60 days (± 3 days), 90 days (± 3 days), and 180 days (± 3 days) after last dose of study drug (last immunization with CDX-1401/poly ICLC/nivolumab) .or until resolution of any drug-related toxicity. Assessment may be collected via telephone if the patient elects to come off study and is no longer coming to clinic.

- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol-specified procedure.
- An SAE report should be completed for any event where doubt exists regarding its seriousness.
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

Investigators MUST report within 1 business day upon becoming aware, to the supporter ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention.

The investigator must inform Bristol Myers Squibb (BMS) and Celldex in writing using a BMS SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celldex by facsimile within 24 hours/1 business day.

- The BMS protocol ID number must be included on whatever form is submitted by the Sponsor/Investigator.

The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report.

Celldex and BMS consider an SAE to be any adverse event that is life-threatening or that results in any of the following outcomes: death; inpatient hospitalization or prolongation of existing hospitalization; persistent or significant disability or incapacity; or a congenital anomaly or birth defect.

Completed SAE reports are to be submitted to:

Bristol-Myers Squibb
SAE Email Address: Worldwide.Safety@BMS.com
SAE Facsimile Number: +1 609-818-3804

AND

Celldex Therapeutics, Inc.
Clinical Research/Operations
Hotline: 908-323-2233
Fax No: 781-644-6434
Email: SAE@celldex.com

17.5.1 Suspected/ Unexpected Serious Adverse Reaction

In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of a SUSAR Report.

- Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (e.g., animal) study, important safety recommendations from a study data monitoring committee, or supporter decision to end or temporarily halt a clinical study for safety reasons.
- Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the Sponsor/Investigator will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
- In addition to the Sponsor Investigator's responsibility to report events to their local HA, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

17.6 Follow-Up for Serious Adverse Events

All related SAEs should be followed to their resolution, until the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible. New information will be reported when it is received.

17.7 Unanticipated Problems

An Unanticipated Problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:
    - The research procedures that are described in the study-related documents, including study deviations, as well as issues related to compromise of participant privacy or confidentiality of data.
    - The characteristics of the participant population being studied.
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized and if in relation to an AE is also deemed Serious per Section 17.3.

Reporting Unanticipated Problems:

Unanticipated problem reporting will begin at the time of participant consent. The Reportable New Information (RNI) Form will be submitted to the CRS Compliance Office within 1 business day of becoming aware of the Unanticipated Problem. After review, CRS Compliance will submit the RNI to the IRB.

When becoming aware of new information about an Unanticipated Problem, submit the updated information to CRS Compliance with an updated Reportable New Information Form. The site Investigator or designated research personnel will report all unanticipated problems to the **IRB in accordance with their local institutional guidelines**.

17.8 FDA Reporting

When RPCI is the IND holder the following describes the FDA reporting requirements by timeline for AEs and new safety findings that meet the criteria outlined below:

Within 7 Calendar Days

Any adverse event that meets **ALL** the following criteria:

- Related or possibly related to the use of the study drug;
- Unexpected; and
- Fatal or life-threatening.

Within 15 Calendar Days

Any adverse event that meets **ALL** the following criteria:

- Related or possibly related to the use of the study drug;
- Unexpected; and
- Serious but not fatal or life-threatening;

Or, meets **ANY** of the following criteria:

- A previous adverse event that is not initially deemed reportable but is later found to fit the criteria for reporting (report within 15 days from when event was deemed reportable).

- Any findings from other studies, including epidemiological studies, pooled analysis of multiple studies, or other clinical studies conducted with the study drug that suggest a significant risk in humans exposed to the drug.
- Any findings from animal or in vitro testing that suggest a significant risk for human participants including reports of mutagenicity, teratogenicity, or carcinogenicity or reports of significant organ toxicity at or near the expected human exposure.
- Any clinically important increase in the rate of occurrence of a serious, related or possibly related adverse event over that listed in the protocol or investigator brochure.

Supporters are also required to identify in IND safety reports, all previous reports concerning similar adverse events and to analyze the significance of the current event in the light of the previous reports.

Reporting Process

The principal investigator or designee will complete and submit a FDA Form 3500A MedWatch for any event that meets the above criteria. Forms will be submitted to the CRS Compliance Office via email to CRSCompliance@RoswellPark.org.

18 DATA MANAGEMENT AND CONFIDENTIALITY

18.1 Data Collection

Full build studies are managed by RPCI CRS Data Management for analysis by RPCI Biostatisticians. All electronic case report form (eCRF) data are captured for these studies.

Data management activities are performed using a CTMS system that enables the collection, cleaning and viewing of clinical trial data. CRS data management designs the study-specific database and facilitates development by the Information Technology team. Once the database design is approved by the Investigator, Statistician, and Clinical Research Coordinator, the database is put into production and data entry can begin. Data can be entered and changed only by those with the rights to do so into the eCRFs.

18.2 Maintenance of Study Documents

Essential documents will be retained per RPCI's policy for 6 years from the study termination date. These documents could be retained for a longer period, however, if required by the applicable local regulatory requirements or by an agreement with RPCI.

18.3 Revisions to the Protocol

RPCI may make such changes to the protocol as it deems necessary for safety reasons or as may be required by the U.S. FDA or other regulatory agencies. Revisions will be submitted to the IRB/ERC for written approval before implementation. Any significant protocol amendments will also be provided to FDA.

18.4 Termination of the Study

It is agreed that, for reasonable cause, either the RPCI Investigators or the supporter, may terminate this study, provided a written notice is submitted within the time period provided for in the Clinical

Trial Agreement. In addition, RPCI may terminate the study at any time upon immediate notice if it believes termination is necessary for the safety of participants enrolled in the study.

18.5 Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

19 STATISTICAL PLAN

This is an open-label, non-randomized, dual center, fixed dose, Phase 1 study of CDX-1401 1 mg + poly-ICLC 1.8 mg (Vaccine) given in conjunction with decitabine 20 mg/m2/d x 5 days and nivolumab 3 mg/kg every 2 weeks. Details of the study design are provided in Section 9.

The primary objective of this study is to evaluate the safety of Anti-DEC-205-NY-ESO-1 fusion protein + poly-ICLC given in combination with decitabine 20 mg/m2 intravenously and nivolumab 3 mg/kg in in patients with MDS or low blast count AML.

19.1 Sample Size Determination

A maximum of 18 evaluable participants will be enrolled in this study. The number of participants required is a function of the unknown relationship between this treatment combination and the toxicity rate. Accrual is expected to take 2-4 years. We expect 18 patients will be accrued, all at Dose Level 1.

The primary statistical endpoint is the proportion of n=12 evaluable patients in the expansion cohort experiencing a DLT. A DLT rate $\geq$0.60 is considered unacceptable.

The DLT rate will be estimated as a binomial proportion of evaluable patients with any DLT. If the upper 1-sided 95% Jeffreys credible interval exceeds 0.60, the protocol therapy will be considered too toxic. With n=12 evaluable patients, this occurs if 5 or more patients experience a DLT. With n=12 evaluable patients, the upper confidence limit is less than 0.60 in 80% of similar experiments when the true DLT rate is 0.27.

19.2 Other Safety Analysis

The primary objective of safety will be quantified using the observed rates of the adverse events, serious adverse events (SAE) and Dose Limiting Toxicities. Toxicity rates will be described using upper 1-sided 95% Jeffreys binomial confidence intervals.

19.3 Efficacy Analysis

All efficacy evaluations will be for correlative measures of immune response. Given the small sample size it will be impossible to compare responses with historical controls or speculate about the response over and above the historical response anticipated with single agent decitabine. Objective responses will be recorded and graded using the International Working Group Criteria for MDS and modified International Working Group Criteria for AML as detailed in Appendix D, Appendix E and, Appendix F.

19.4 Secondary Analysis

The secondary objectives consider immune and molecular epigenetic response to treatment. Levels of CD8+ and CD4+ T cells, NYESO-1 specific antibodies, and other quantitative variables will be measured at baseline (before treatment) and at designated time points during treatment. These measures will be summarized by descriptive statistics (means, medians, quartiles, etc.). Confidence intervals will be constructed for the median and the mean. Exploratory graphical analysis will be used to discover associations among variables.

The statistical significance of the change in marker values resulting from treatment will be assessed using the (paired sample) Wilcoxon Signed Rank test. With a significance threshold of 0.05 and two observations (pre/post) for each of 18 patients, this test has 80% power to detect a shift in means of at least 1.1 standard deviations.

19.5 Demographics and Baseline Characteristics

Descriptive statistics (as appropriate: n, percent, mean, median, min and max) will be used to summarize demographic and baseline characteristics.

19.5.1 Adverse Event

The frequency of toxicities will be tabulated by grade across all dose levels and cycles. The frequency of toxicities will also be tabulated for the dose estimated to be the MTD/MAD. All participants who receive any study treatment will be considered evaluable for toxicity.

19.6 Correlative Data Analysis

Epigenetic and immunologic response outcomes will be measured at baseline (before treatment) and at designated time points during treatment. These measures will be summarized by descriptive statistics (means, medians, quartiles etc.). Confidence intervals will be constructed for the median and the mean. Exploratory graphical analysis will be used to discover associations among variables.

20 PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS

The Early Phase Clinical Trials Committee will assess the progress of the study, the safety data, and critical efficacy endpoints. The EPCTC will review the study annually and will make recommendations that include but not limited to; (a) continuation of the study, (b) modifications to the design (c) or termination of the study.

21 VULNERABLE POPULATIONS

Not Applicable. Refer to Section 3.3: Special Populations.

22 COMMUNITY-BASED PARTICIPATORY RESEARCH

Not Applicable

23 SHARING OF RESULTS WITH SUBJECTS

Individual response data is shared with the participant as a part of their clinical care.

24 SETTING

Potentially eligible patients will be recruited from the population of newly diagnosed MDS patients referred to the treating centers. Patients will have a suspected or known diagnosis of MDS or low blast count AML with MDS related changes and be appropriate for primary therapy with a hypomethylating agent (HMA).

Potential study participants will be identified and recruited from current Leukemia Service patients and from community referral.

25 PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF SUBJECTS

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

26 RESOURCES AVAILABLE

Not Applicable

27 PRIOR APPROVALS

Not Applicable

28 COMPENSATION FOR RESEARCH-RELATED INJURY

Please refer to the informed consent form (Section 13) related to this study:

29 ECONOMIC BURDEN TO SUBJECTS

The participant and /or their insurance company will be responsible for charges related to the administration of drugs used in this clinical research study and for charges for medications that may be needed to prevent or control side effects.

30 CONSENT PROCESS

This study will not be initiated until the protocol and informed consent document(s) have been reviewed and approved by a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Each participant (or legal guardian) shall read, understand, and sign an instrument of informed consent prior to performance of any study-specific procedure. It is the responsibility of the investigator to ensure that the participant is made aware of the investigational nature of the treatment and that informed consent is given.

The Investigator is responsible for the retention of the participant log and participant records; although personal information may be reviewed by authorized persons, that information will be treated as strictly confidential and will not be made publicly available. The investigator is also responsible for obtaining participant authorization to access medical records and other applicable study specific information according to Health Insurance Portability and Accountability Act regulations (where applicable).

This study will be conducted in compliance with all applicable laws and regulations of the state and/or country and institution where the participant is treated. The clinical trial should be conducted in accordance with the ethical principles embodied in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, consistent with good clinical practice and the applicable regulatory requirements and according to the guidelines in this protocol, including attached appendices.

31 PROCESS TO DOCUMENT CONSENT IN WRITING

The Investigator (or IRB specified designee) is responsible for obtaining written consent from each participant or the participant's legally authorized representative in accordance with GCP guidelines using the approved informed consent form, before any study specific procedures (including screening procedures) are performed. The informed consent form acknowledges all information that must be given to the participant according to applicable GCP guidelines, including the purpose and nature of the study, the expected efficacy and possible side effects of the treatment(s), and specifying that refusal to participate will not influence further options for therapy. Any additional information that is applicable to the study must also be included. Additional national or institutionally mandated requirements for informed consent must also be adhered to. The participant should also be made aware that by signing the consent form, processing of sensitive clinical trial data and transfer to other countries for further processing is allowed.

The Investigator or designee shall provide a copy of the signed consent form to the participant and the signed original shall be maintained in the Investigator File. A copy of the signed consent form must be filed in the participant file. At any stage, the participant may withdraw from the study and such a decision will not affect any further treatment options.

32 DRUGS OR DEVICES

32.1 Vaccine (Anti DEC-205-NY-ESO-1 Fusion Protein (CDX-1401)/ Poly ICLC)

32.1.1 Active Substance and Source

CDX-1401

The clinical trial product will be formulated as a sterile solution intended for parenteral use. CDX-1401 will be provided in 2 ml vials containing approximately 1 ml of solution, at a concentration of 1 mg/ml.

Poly-ICLC

Poly-ICLC is an Investigational Product manufactured by Dalton for Oncovir, Inc. and supplied by Oncovir, Inc.

Poly-ICLC (polyinosinic-polycytidylic acid stabilized with poly-L-lysine and carboxymethylcellulose) is a synthetic double-stranded ribonucleic acid (dsRNA) with broad immune-enhancing effects mediated through TLR-3 activation.

Poly-ICLC will be provided in single-dose vials containing 1 ml of 1.8 mg/ml opalescent solution.

The poly-ICLC vials should be refrigerated at about 40ºF (2-8ºC) but should not be frozen. Poly-ICLC is also stable at room temperature for brief periods (days).

Because the product is not formulated with a preservative, once the sterile vials are entered or the poly-ICLC is drawn into a syringe, the drug should be used as soon as possible (typically within 6 hours if kept at room temperature or within 24 hours if refrigerated and the syringe(s) had been filled under aseptic conditions) or in accordance with any applicable institutional guidance. Poly-ICLC is to be withdrawn from the vial under sterile conditions and administered subcutaneously as supplied.

32.1.2 Drug Shipment

Clinical grade DEC205mAb-NY-ESO-1 fusion protein (CDX-1401) and poly-ICLC (manufactured by Dalton for Oncovir, Inc. and provided by Oncovir, Inc., Inc through their agreement with Celldex Therapeutics) are supplied by Celldex Therapeutics Inc., Fall River, MA. CDX-1401 will be provided by the company and shipped to the participating sites.

The date of receipt and the amount of drug received will be documented. Drug shipment records will be retained by the investigational pharmacist or designee.

32.1.3 Preparation

CDX-1401 will be provided as a 1 mg/mL solution. It will be given intracutaneously as outlined in Section 10.

32.1.4 Storage and Stability

The Investigator or designate will be responsible for ensuring that the investigational product is securely maintained in a locked, limited-access facility, as specified and, in accordance with the applicable regulatory requirements.

CDX-1401 vials should be stored at -20 ± 5˚C.

Once thawed, vials should be stored at 2 to 8°C and used within 7 days. Vials left at room temperature should be used within 24 hours. Celldex should be contacted if thawed vials are stored at 2 to 8° C for more than 7 days or at room temperature for more than 24 hours.

CDX-1401 is not formulated with a preservative. Therefore, once the sterile vials are entered (i.e., once CDX-1401 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).

Drug storage temperature will be maintained and recorded, as applicable.

32.1.5 Handling and Disposal

The Investigator or designee will be responsible for dispensing and accounting for all investigational drug provided by the Supporter exercising accepted medical and pharmaceutical practices. Study drugs must be handled as cytotoxic agents and appropriate precautions taken per the institution’s environmentally safe handling procedures. All investigational drugs will be dispensed in accordance with the Investigator’s prescription or written order.

All products dispensed will be recorded on a product accountability record. Records of product lot numbers and dates received will be entered on a product accountability form. This record will be reviewed by the Supporter’s staff or representative during periodic monitoring visits. It is the

Investigator's responsibility to ensure that an accurate record of investigational drug issued and returned is maintained.

Used vials (excess drug) will be destroyed according to standard practices after properly accounting for the dispensing. Partially used vials of study drug will not be re-used for other participants.

Under no circumstances will the Investigator supply investigational drug to a third party or allow the investigational drug to be used in a manner other than as directed by this protocol.

32.2 Nivolumab

32.2.1 Active Substance and Source

Nivolumab Injection, 100 mg/10 mL (10 mg/mL), is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentaacetic acid (pentetic acid), and polysorbate 80 (Tween™ 80), pH 6.0 and includes an overfill to account for vial, needle, and syringe holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals.

32.2.2 Drug Shipment

Nivolumab will be provided by Bristol-Myers Squibb and shipped to the participating site.

The date of receipt and the amount of drug received will be documented. Drug shipment records will be retained by the investigational pharmacist or designee.

32.2.3 Preparation

During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

32.2.4 Storage and Stability

The Investigator or designate will be responsible for ensuring that the investigational product is securely maintained in a locked, limited-access facility, as specified and, in accordance with the applicable regulatory requirements.

Vials of nivolumab injection must be stored at 2C to 8C (36°F to 46°F) and protected from light and freezing.

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

Drug storage temperature will be maintained and recorded, as applicable.

32.2.5 Handling and Disposal

The Investigator or designee will be responsible for dispensing and accounting for all investigational drug provided by Bristol-Myers Squibb (BMS), exercising accepted medical and pharmaceutical practices. Study drugs must be handled as cytotoxic agents and appropriate precautions taken per the institution's environmentally safe handling procedures. All investigational drugs will be dispensed in accordance with the Investigator's prescription or written order.

All products dispensed will be recorded on a product accountability record. Records of product lot numbers and dates received will be entered on a product accountability form. This record will be reviewed by the Supporter's staff or representative during periodic monitoring visits. It is the Investigator's responsibility to ensure that an accurate record of investigational drug issued and returned is maintained.

Used vials (excess drug) will be destroyed according to standard practices after properly accounting for the dispensing. Partially used vials of study drug will not be re-used for other participants.

Under no circumstances will the Investigator supply investigational drug to a third party or allow the investigational drug to be used in a manner other than as directed by this protocol.

32.3 Decitabine

Decitabine is commercially available and will be dispensed per standard of care. Decitabine will not be provided by this study and will be paid for by the patient's insurance carrier as part of the standard of care treatment.

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34 APPENDICES/SUPPLEMENTS

Appendix A ELIGIBILITY VERIFICATION FORM: INCLUSION CRITERIA

Participant Name: (Network sites use participant initials): _____

Medical Record No.: (Network sites use participant ID): _____

Title: A Phase 1 Study of DEC205mAb-NY ESO 1 Fusion Protein (CDX-1401) given with Adjuvant Poly-ICLC in Conjunction with 5-Aza-2'deoxycytidine (Decitabine) and Nivolumab in Patients with MDS or Low Blast Count AML

INCLUSION CRITERIA				
Yes	No	N/A	All answers must be "Yes" or "N/A" for participant enrollment.	Date
☐	☐	☐	1. Have a confirmed diagnosis of: a. IPSS intermediate-1, intermediate-2 or high-risk MDS including Chronic Myelomonocytic Leukemia (CMML) **OR** b. Low blast count AML with ≤ 30% blasts previously classified as Refractory Anemia with excess blasts in transformation.	
☐	☐	☐	2. Age ≥ 18 years of age.	
☐	☐	☐	3. Have an ECOG Performance Status of ≤ 2. Refer to Appendix "C".	
☐	☐	☐	4. Have adequate organ function defined by the following laboratory values: • Hepatic: o Total bilirubin ≤ 3 X upper limit of normal (ULN) (except subjects with Gilbert Syndrome, who can have total bilirubin up to 3.5 X ULN) o Aspartate Transaminase (AST/SGOT) and Alanine Transaminase (ALT/SGPD) ≤ 3 X ULN • Renal: o Serum creatinine ≤ 2.5 X ULN • Cardiac: o Troponin-I, CK-MB≤ ULN o LVEF ≥ LLN (institutional limit)	
☐	☐	☐	5. Participants of child-bearing potential must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 6 months after the last treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.	
☐	☐	☐	6. Participant or legal representative must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.	
☐	☐	☐	7. No prior exposure to nivolumab.	

PROTOCOL TITLE: I 49217 - Phase 1 CDX-1401/ Poly-ICLC +Decitabine +Nivolumab in Patients with MDS or Low Blast Count AML

INCLUSION CRITERIA				
Yes	No	N/A	All answers must be "Yes" or "N/A" for participant enrollment.	Date
☐	☐	☐	8. No prior investigational therapy within 2 weeks prior to study enrollment	

Investigator Signature: _____ **Date:** _____

Printed Name of Investigator: _____

Appendix B ELIGIBILITY VERIFICATION FORM: EXCLUSION CRITERIA

Participant Name: (Network sites use participant initials): _____

Medical Record No.: (Network sites use participant ID): _____

Title: A Phase 1 Study of DEC205mAb-NY ESO 1 Fusion Protein (CDX-1401) given with Adjuvant Poly-ICLC in Conjunction with 5-Aza-2'deoxycytidine (Decitabine) and Nivolumab in Patients with MDS or Low Blast Count AML

EXCLUSION CRITERIA				
Yes	No	N/A	All answers must be "No" or "N/A" for participant enrollment.	Date
☐	☐	☐	1. Subjects with life-threatening illnesses other than MDS, uncontrolled medical conditions or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, or put the study outcomes at risk.	
☐	☐	☐	2. AML associated with inv(16); t(16;16); t(8;21) or t(15;17).	
☐	☐	☐	3. Previously untreated MDS with isolated del5q (for which lenalidomide is approved an approved therapy) and chronic myelomonocytic leukemia (CMML) with rearrangements of the PDGF receptor (for which imatinib is approved therapy), unless they have previously failed these approaches.	
☐	☐	☐	4. Subjects with symptomatic central nervous system (CNS) disease which is not adequately controlled	
☐	☐	☐	5. Subjects who have received prior radiation therapy for extramedullary disease within 2 weeks of first dose.	
☐	☐	☐	6. Has known immunosuppressive disease (e.g. HIV, AIDS or other immune depressing disease). Testing is not required, only to be done for a possible diagnosis which is not confirmed.	
☐	☐	☐	7. 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. In addition, subjects will be excluded for any of the following: • Myocardial infarction or arterial or venous thromboembolic events within 6 months prior to baseline or severe or unstable angina, New York Heart Association (NYHA) Class III or IV disease • Active congestive heart failure (New York Heart Association functional classification III or IV). • Documented history of cardiomyopathy with EF< 30%. • Uncontrolled hypertension (SBP>160/DBP>100 despite medical intervention).•History of myocarditis of any etiology	
☐	☐	☐	8. Subjects who have hypersensitivity to decitabine, CDX-1401, poly-	

PROTOCOL TITLE: I 49217 - Phase 1 CDX-1401/ Poly-ICLC +Decitabine +Nivolumab in Patients with MDS or Low Blast Count AML

EXCLUSION CRITERIA				
Yes	No	N/A	All answers must be "No" or "N/A" for participant enrollment.	Date
			ICLC or nivolumab.	
☐	☐	☐	9. History of auto-immune disease (e.g., thyroiditis, lupus), except vitiligo.	
☐	☐	☐	10. Pregnant or nursing female subjects.	
☐	☐	☐	11. Unwilling or unable to follow protocol requirements.	
☐	☐	☐	12. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive study drug.	
☐	☐	☐	13. Regular use of immunosuppressant drugs such as steroids (>20mg prednisone equivalents), azathioprine, tacrolimus, cyclosporine, etc. Use is not permitted within 4 weeks before recruitment.	

Participant meets all entry criteria: ☐ **Yes** ☐ **No**
If "NO", do not enroll participant in study.

Investigator Signature: _____ **Date:** _____

Printed Name of Investigator: _____

Appendix C ECOG Performance Status Scores

Description	Status
Fully active, able to carry on all pre-disease performance without restriction.	0
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.	1
Ambulatory and capable of all self-care but unable to carry out any work activities.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4
Dead	5

Appendix D Response Criteria for MDS and AML According to Modified International Working Group Criteria

Response Criteria for MDS and AML patients according to modified IWG criteria	
Designation	**Criteria for Response**
Morphologic Leukemia Free state	<5% blasts in the marrow
Complete Response (CR)	Morphologic CR: BM blasts <5% with no dysplasia, in combination with CBC demonstrating: 1) platelets > 100K/mm^3, 2) neutrophils > 1000/mm^3 Cytogenetic CR: As above + cytogenetics normal Molecular CR: As above + Molecular testing negative
Partial Remission (PR)	For MDS: BM blasts decreased by ≥50%, or less advanced MDS FAB classification than pretreatment. For AML: Blasts decreased by ≥50% or decrease to 5-25; Blasts ≤ 5% if Auer rod positive Platelets >100,000
Stable Disease (SD)	No PR, but no evidence of progression ≥ 2 months
Hematological Improvement (HI)	Erythroid Response (HI-E) 1) Major: Transfusion independence or 2g increase in Hg 2) Minor: 1 to 2g increase in Hg or 50% decrease in transfusion requirements Platelet Response (HI-P) 1) Major: absolute increase in platelets of 30K/mm^3 or development of transfusion independence 2) Minor 50% increase, net 10-30K/mm^3 Neutrophil Response (HI-N) 1) Major: 100% increase or absolute increase ≥500/mm^3 2) Minor: 100% increase with value ≤500/mm^3

1. Cheson BD, Bennett JM, Kopecky KR, Buchner T, Willman CL, Estey EH, Schiffer CA, Doehner H, Tallman MS, Lister TA, Lo-Coco F, Willemze R, Biondi A, Hiddemann W, Larson RA, Lowenberg B, Sanz MA, Head DR, Ohno R, Blomfield CD. Revised recommendations of the international working group for diagnosis, standardization of response criteria, treatment outcomes and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol 2003; 21:4642-4649.

2. Cheson BD, Bennett JM, Kantarjian H, Pinto A, Schiffer CA, Nimer SD, Lowenberg B, Beran M, de Witte TM, Stone RM, Mittelman M, Sanz GF, Wijermans PW, Gore S, Greenberg PL, World Health Organization(WHO) international working group: Report of an international

working group to standardize response criteria for myelodysplastic syndromes. Blood 2000;96:3671-3674.

3. Cheson BD, Cassileth PA, Head DR, Schiffer CA, Bennett JM, Bloomfield CD, Brunning R, Gale RP, Grever MR, Keating MJ: Report of the National Cancer Institute-sponsored workshop on definitions of diagnosis and response in acute myeloid leukemia. J Clin Oncol 1990;8:813-819.

Appendix E International Prognostic Scoring System for MDS

Variable					
Score	0	0.5	1.0	1.5	2.0
BM Blasts	<5	5-10		11-20	31-30
Karyotype	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

Risk Group	Score	Med Survival (y)	25% AML progression (y)
Low	0	5.7	9.4
Int-1	0.5-1.0	3.5	3.3
Int-2	1.5-2.0	1.1	1.1
High	>2.5	0.4	0.2

- Cytopenias are designated by the following: ANC<1800, platelets< 100K, Hg<10g
- Karyotype risk groups:
    - Good: Normal (46 XX or 46 XY), isolated -Y, isolated del(5q), or isolated del(20q)
    - Intermediate: All karyotypes not otherwise designated good or poor
    - Poor: complex karyotype (≥3 abnormalities) or any chromosome 7 abnormalities

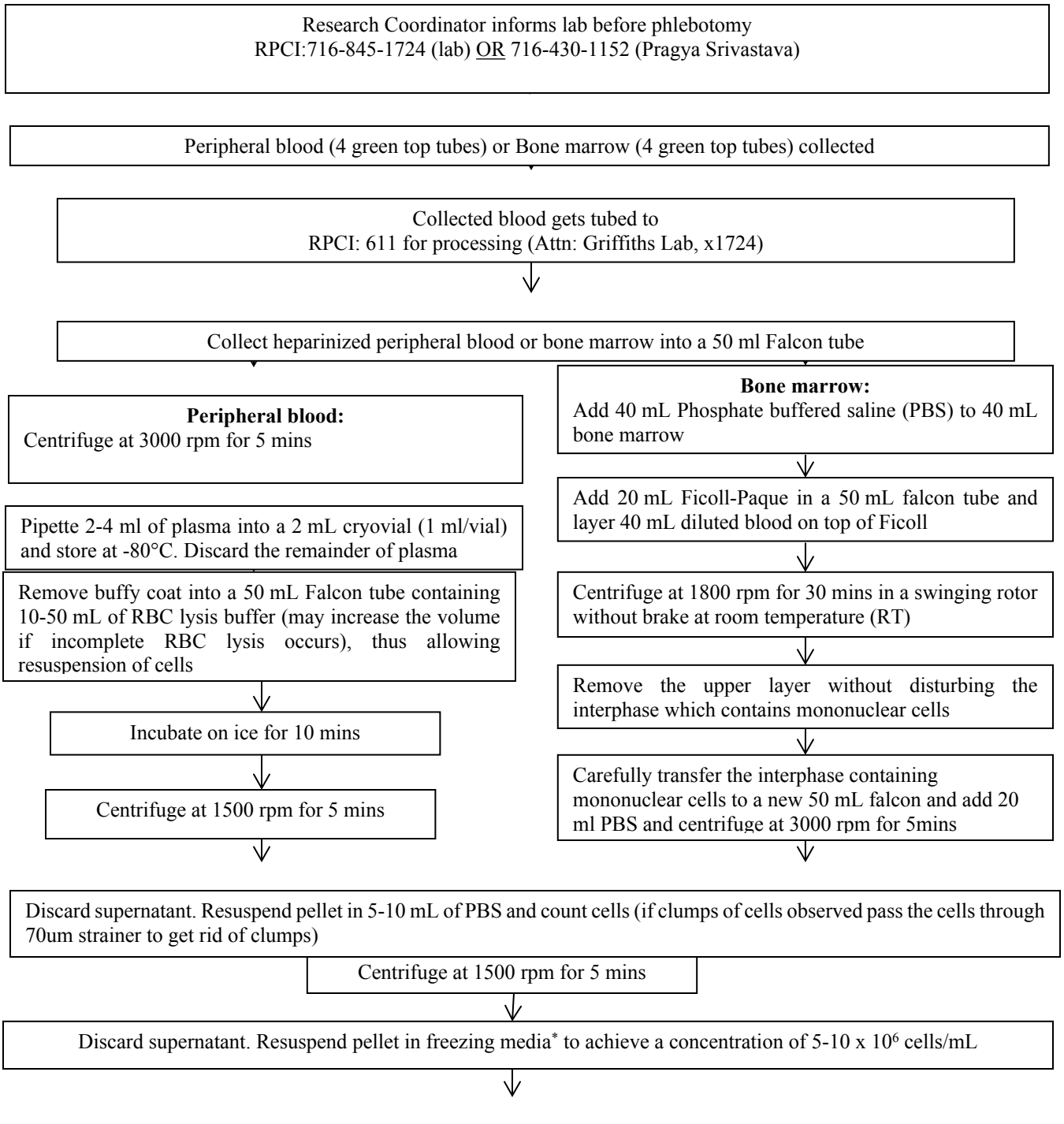
Appendix F Revised International Prognostic Scoring System

Prognostic Group	Cytogenetic Abnormality
Very Good	-Y, del(11q)
Good	NL, del(5q), del(20q), ≤2 w/del (5q)
Int	del(7q), +8, +19, i(17q), any other ≤2 clones
Poor	-7, inv(3)/t(3q)/del(3q), ≥2 w/ -7/del(7q), complex ≤3
Very Poor	Complex (> 3 abnormalities)

Variable	0	0.5	1	1.5	2	3	4
cytogenetics	VG		G		I	P	VP
BM blasts%	≤2		>2-<5		5-10	>10	
Hg (g)	≥10		8-10	<8			
Platelets(/uL)	≥100K	50-100K	<50				
ANC (/uL)	≥0.8	<0.8					

Risk Group	Score	Survival (y)	25% AML Tx (y)
V. Low	≤1.5	8.8	NR
Low	>1.5-3	5.3	10.8
Int	>3-4.5	3.0	3.2
High	>4.5-6	1.6	1.4
V. High	>6	0.8	0.73

Appendix G Sample Processing



Appendix H Manag ed Adverse Events

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical . The guidance applies to all immuno-oncology agents and

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

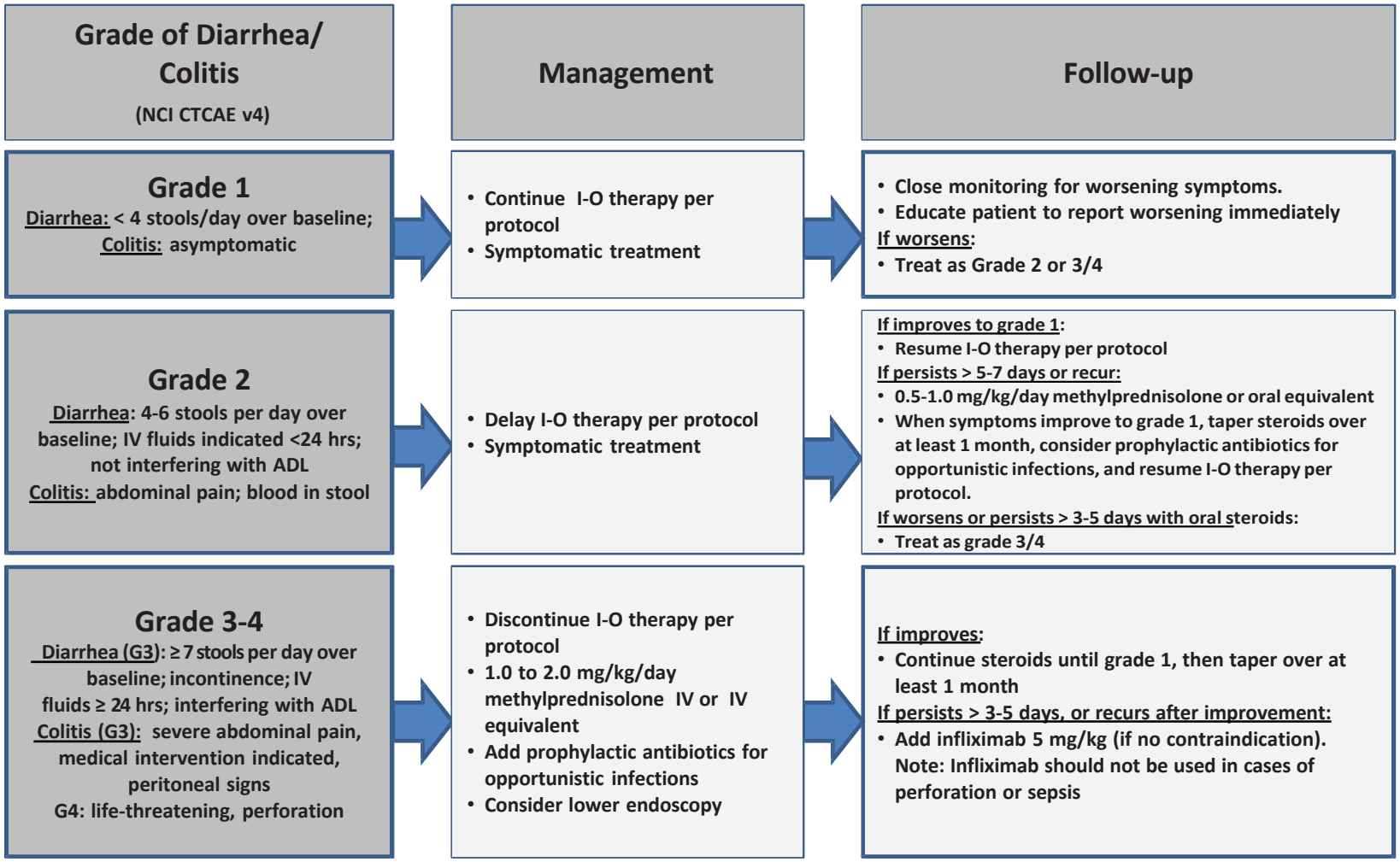
The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

Algorithms (Nivolumab Investigator Brochure, v16, Appendix 3):

- GI Adverse Event Management Algorithm
- Renal Adverse Event Management Algorithm
- Pulmonary Adverse Event Management Algorithm
- Hepatic Adverse Event Management Algorithm
- Endocrinopathy Management Algorithm
- Skin Adverse Event Management Algorithm
- Neurological Adverse Event Management Algorithm

GI Adverse Event Management Algorithm

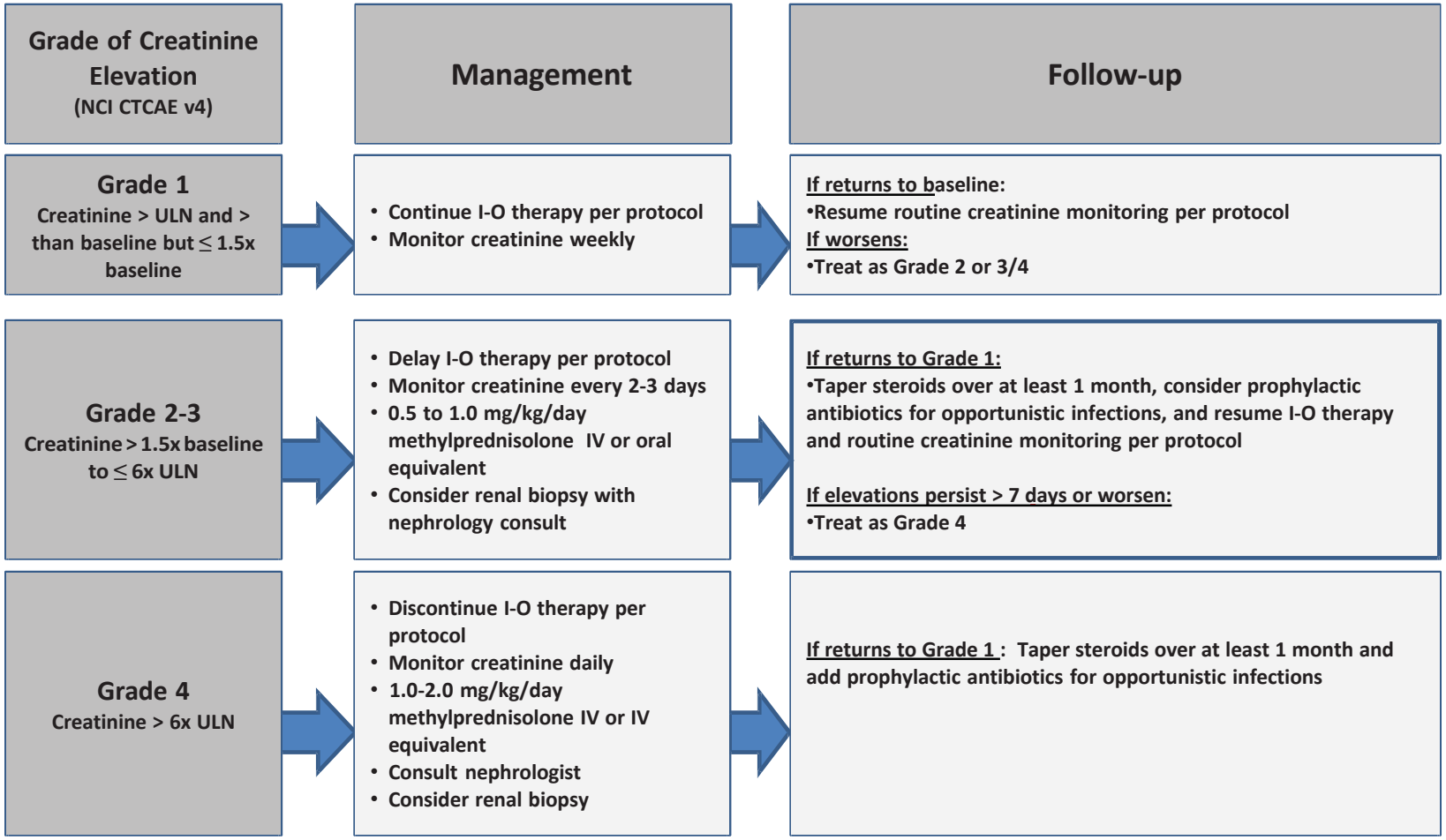
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy.
Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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.

Renal Adverse Event Management Algorithm

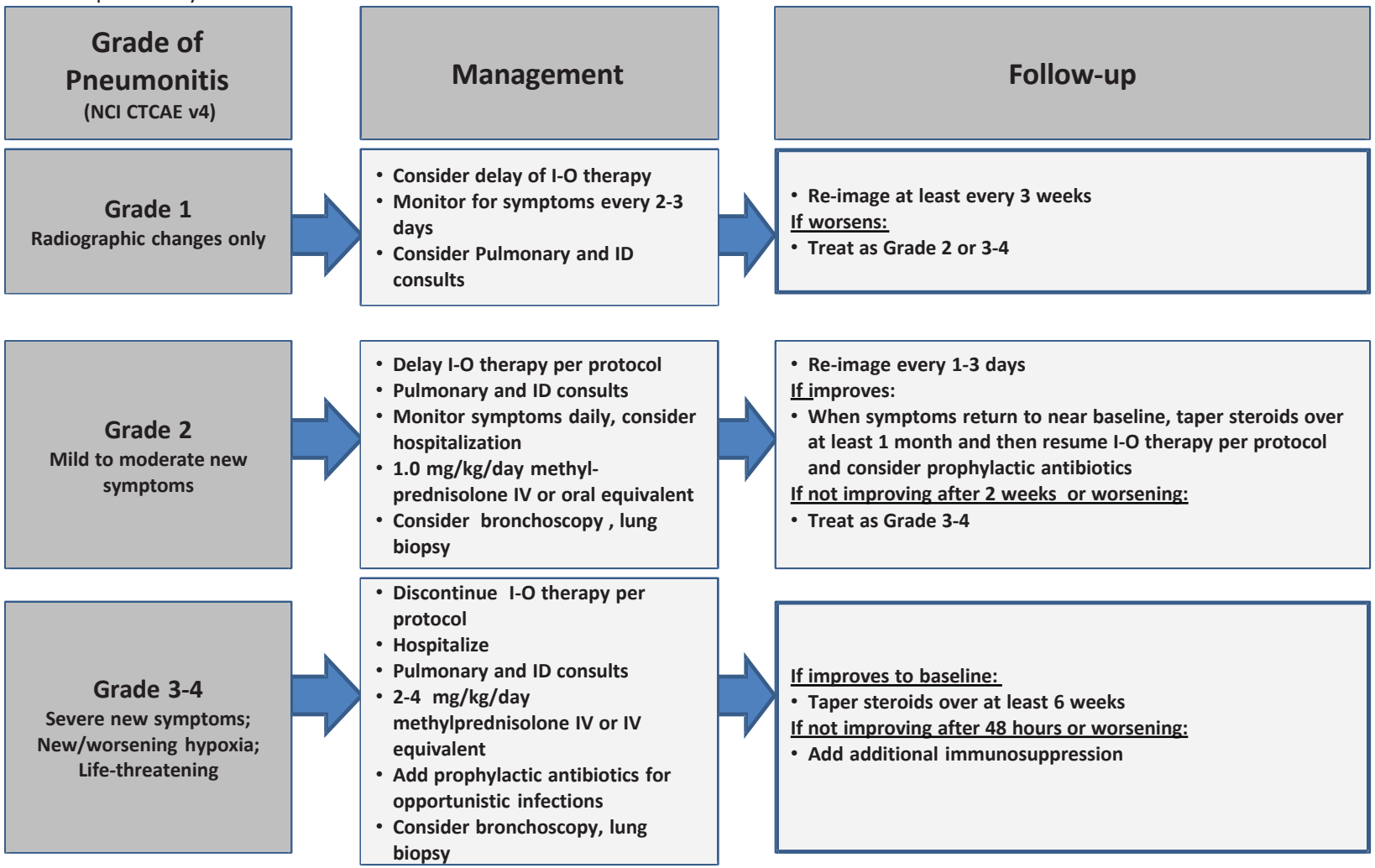
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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.

Pulmonary Adverse Event Management Algorithm

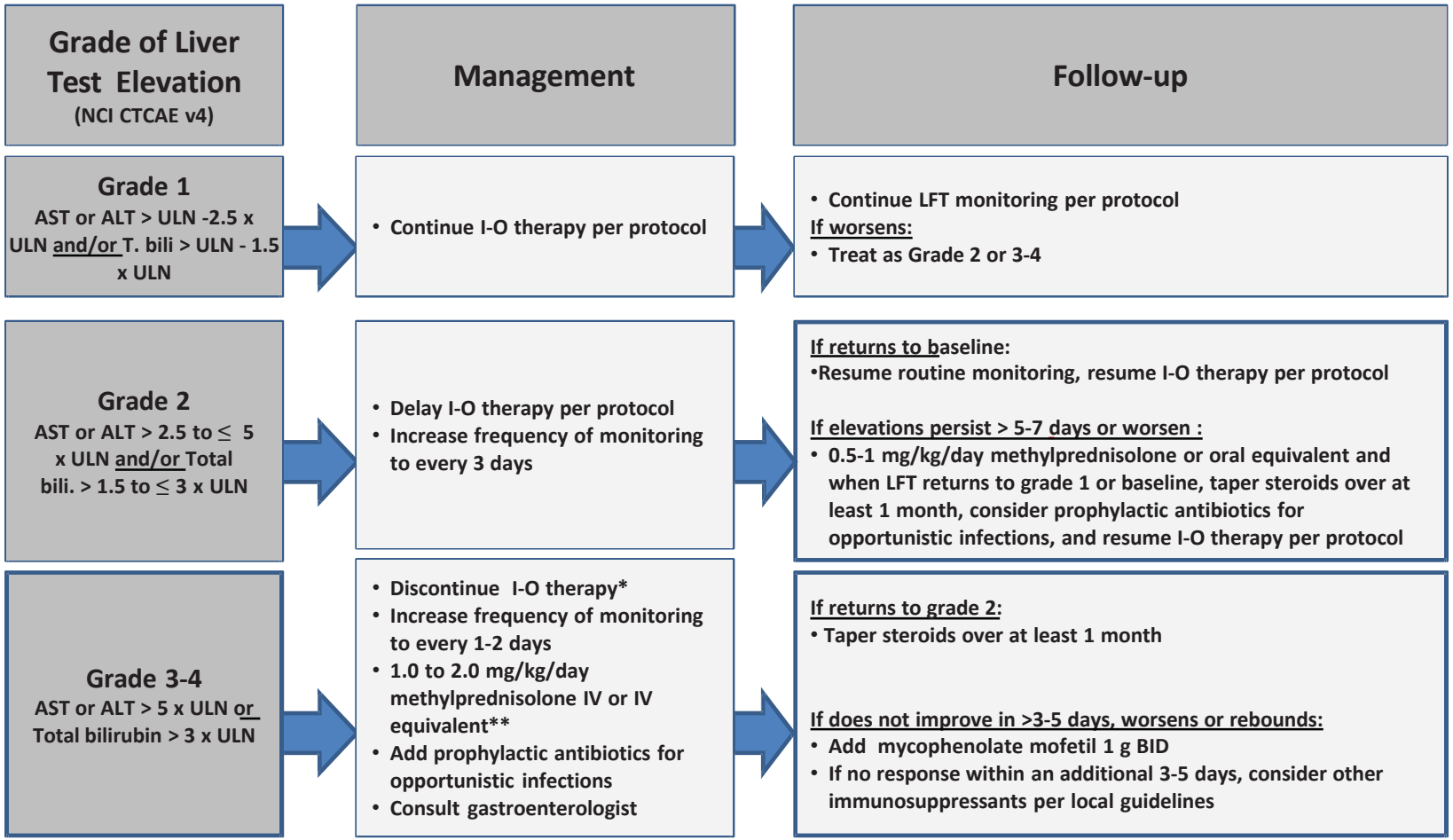
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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.

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.



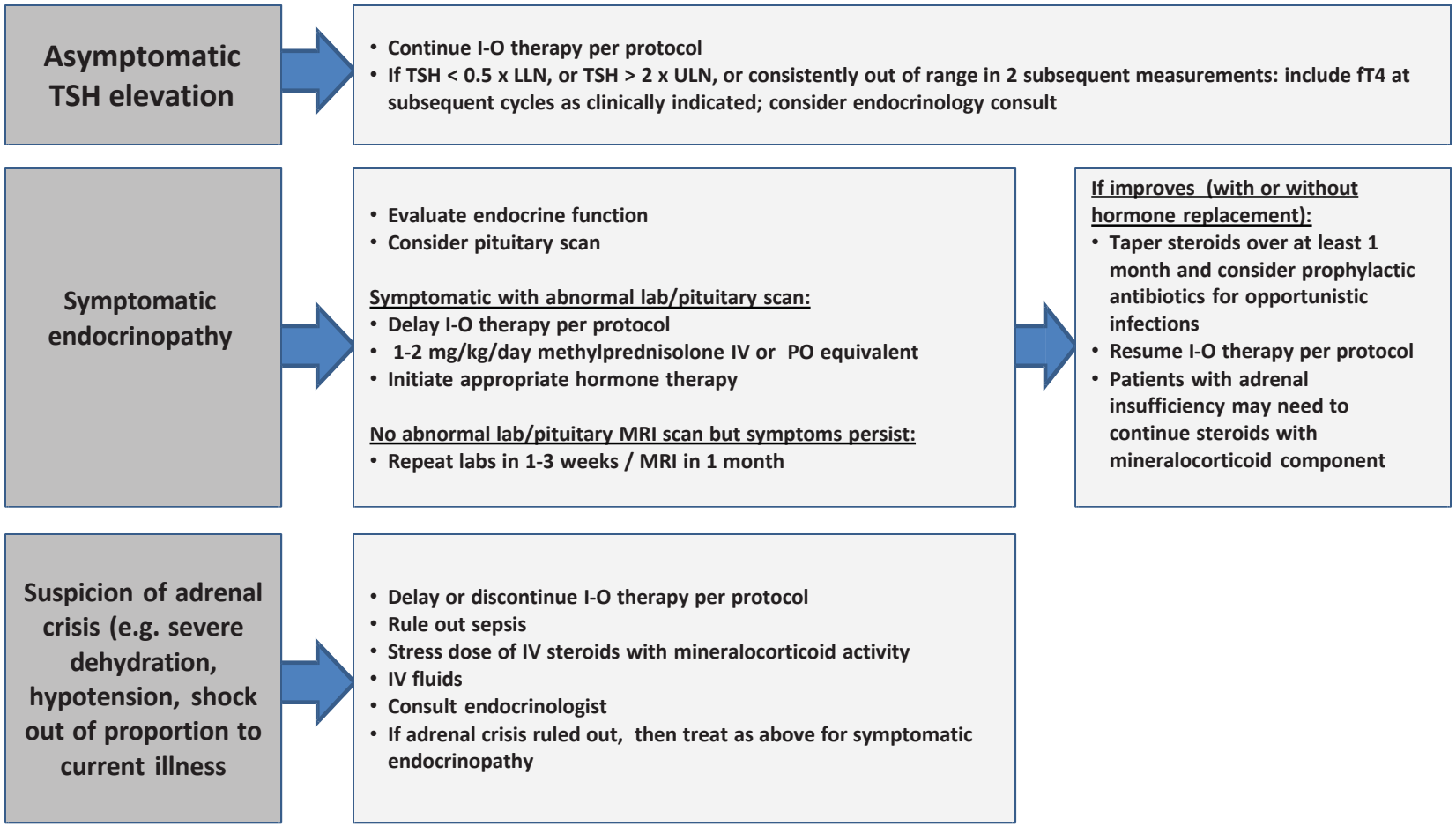
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

Endocrinopathy Management Algorithm

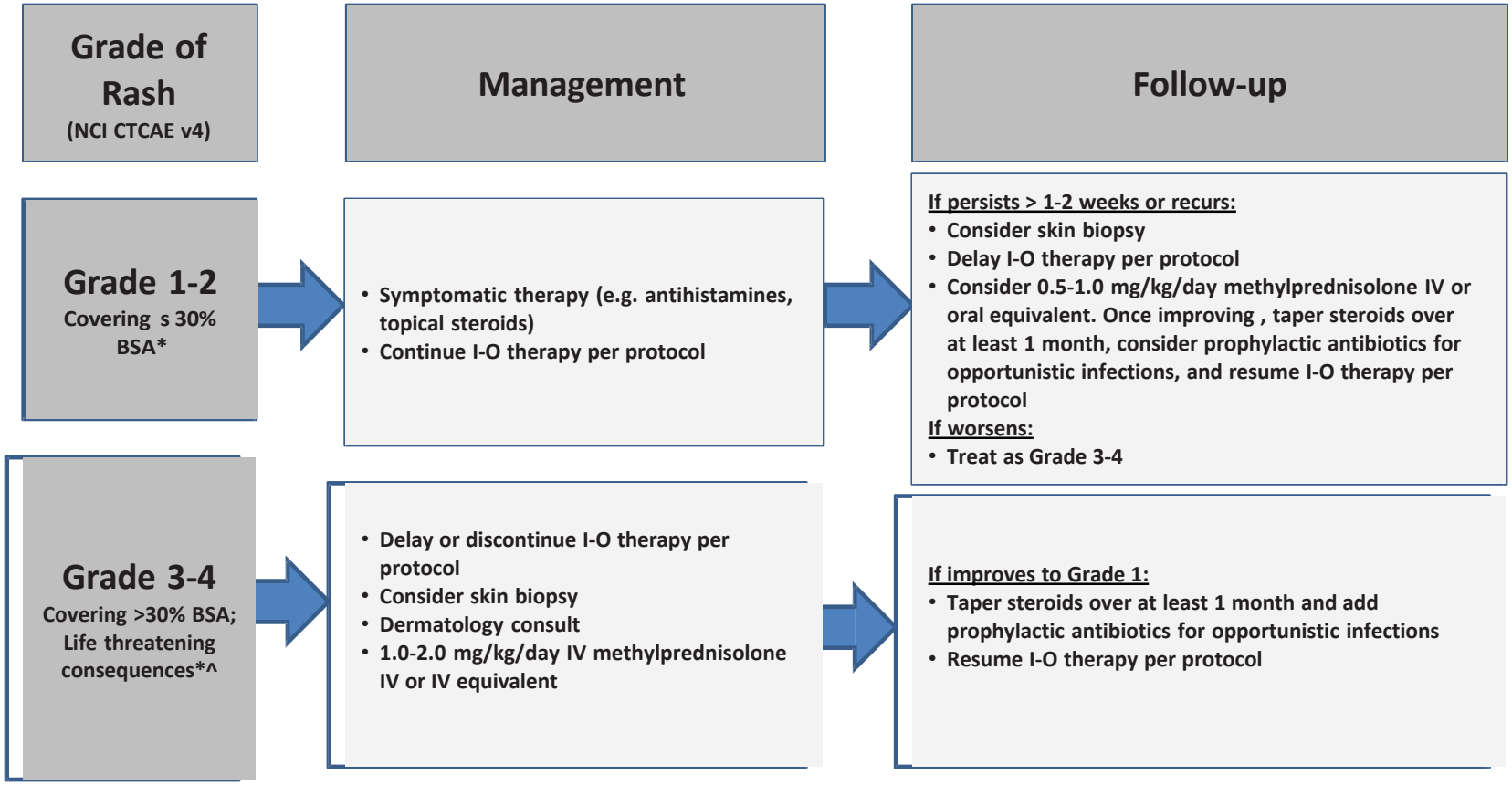
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

Skin Adverse Event Management Algorithm

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



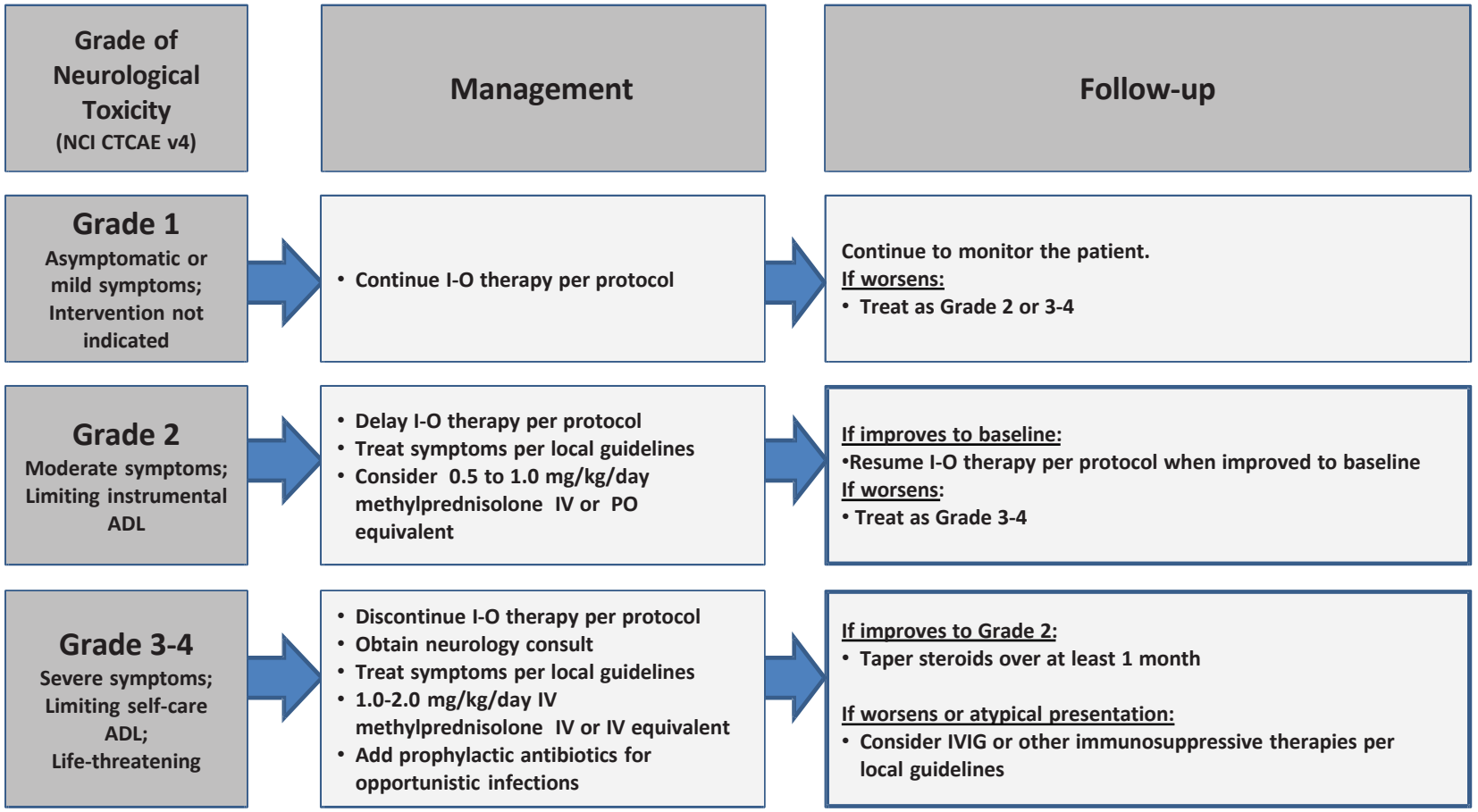
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm

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



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

Appendix I Nivolumab Monotherapy Adverse Drug Reactions

Adverse drug reactions in patients treated with nivolumab monotherapy in clinical studies (N= 9, 212), Investigator Brochure, v16, Table 5.6.1-1.

System Organ Class	Preferred Term	Overall Frequency N (%)	Serious ADRs N (%)	Life Threatening ADRs N (%)	Fatal ADRs N (%)
Cardiac Disorder	Tachycardia	Uncommon 17 (0.18)	n	n	n
	Arrhythmia (including Ventricular arrhythmia, atrial fibrillation [a])	Uncommon 9 (0.10)	**Y** 3 (0.03)	n	n
Ear and Labyrinth Disorders	Vertigo	Uncommon 22 (0.24)	n	n	n
Endocrine Disorders	Hypothyroidism (including Autoimmune hypothyroidism)	Common 443 (4.81)	**Y** 14 (0.14)	n	n
	Hyperthyroidism	Common 141 (1.53)	**Y** 5 (0.05)	n	n
	Hyperglycemia	Uncommon 72 (0.78)	**Y** 16 (0.17)	**Y** [b] 1 (0.01)	n
	Adrenal Insufficiency	Uncommon 52 (0.56)	**Y** 28 (0.31)	**Y** [b] 1 (0.01)	n
	Thyroiditis (including Autoimmune thyroiditis)	Uncommon 36 (0.39)	**Y** [b] 1 (0.01)	n	n
	Hypophysitis	Uncommon 32 (0.35)	**Y** 16 (0.17)	n	n
	Diabetes mellitus	Uncommon 19 (0.21)	**Y** 4 (0.04)	n	n
	Hypopituitarism	Uncommon 16 (0.17)	**Y** 5 (0.05)	n	n
	Diabetic ketoacidosis	Rare 3 (0.03)	**Y** 3 (0.03)	**Y** [b] 1 (0.01)	n
Eye Disorders	Dry eye [a]	Uncommon 42 (0.46)	n	n	n
	Vision blurred [a]	Uncommon 32 (0.35)	n	n	n
	Uveitis (including iridocyclitis)	Uncommon 15 (0.16)	**Y** 3 (0.03)	n	n
Gastrointestinal	Diarrhea	Common	**Y**	n	n

System Organ Class	Preferred Term	Overall Frequency N (%)	Serious ADRs N (%)	Life Threatening ADRs N (%)	Fatal ADRs N (%)
Disorders		783 (8.50)	68 (0.74)		
	Nausea	Common 783 (8.50)	**Y** 23 (0.25)	n	n
	Vomiting	Common 700 (7.60)	**Y** 26 (0.28)	n	n
	Constipation	Common 223 (2.42)	n	n	n
	Abdominal Pain	Common 222 (2.41)	**Y** 13 (0.14)	n	n
	Stomatitis (including Mucosal inflammation, Mucosal ulceration, Mouth ulceration)	Common 159 (1.73)	**Y** 9 (0.10)	n	n
	Dry mouth	Common 157 (1.70)	n	n	n
	Colitis (including Autoimmune colitis)	Common 103 (1.12)	**Y** 72 (0.78)	n	**Y** 2 (0.02)
	Pancreatitis(including Autoimmune pancreatitis, Pancreatitis acute	Uncommon 19 (0.21)	**Y** 10 (0.11)	n	n
	Gastritis (including Gastritis erosive)	Uncommon 16 (0.17)	**Y** 4 (0.04)	n	n
General disorders and administration site conditions	Fatigue (including Asthenia)	Very Common 1701 (18.47)	**Y** 30 (0.33)	n	n
	Pyrexia	Common 326 (3.54)	**Y** 41 (0.45)	n	n
	Edema (including Edema peripheral, Generalized edema, Peripheral swelling, Localized edema, Periorbital edema, Face edema, Swelling face)	Common 182 (1.98)	**Y** 5 (0.05)	n	n
	Chills [a]	Common 146 (1.58)	**Y** 4 (0.04)	n	n
Hepatobiliary Disorders	Hepatitis (including Autoimmune hepatitis, Hepatitis acute)	Uncommon 32 (0.35)	**Y** 25 (0.27)	**Y** [b] 1 (0.01)	n
Immune System Disorders	Infusion related reaction	Common 152 (1.65)	**Y** 21 (0.23)	**Y** [b] 1 (0.01)	n
	Hypersensitivity	Uncommon 70 (0.76)	**Y** 9 (0.10)	**Y** [b] 1 (0.01)	n
	Anaphylactic reaction	Rare 4 (0.04)	**Y** 3 (0.03)	**Y** [b] 2 (0.02)	n
Infections and Infestations	Upper respiratory tract infection	Uncommon 31 (0.34)n	n	n	n
	Bronchitis	Common	n	n	n

System Organ Class	Preferred Term	Overall Frequency N (%)	Serious ADRs N (%)	Life Threatening ADRs N (%)	Fatal ADRs N (%)
		10 (0.11)			
Investigations	Aspartate aminotransferase increased	Common 257 (2.79)	Y 23 (0.25)	n	n
	Alanine aminotransferase increased	Common 239 (2.59)	Y 27 (0.29)	n	n
	Lipase increased	Common 163 (1.77)	Y 13 (0.14)	n	n
	Blood alkaline phosphatase increased [a]	Common 127 (1.38)	**Y** 6 (0.07)	n	n
	Amylase increased	Common 102 (1.11)	**Y** 4 (0.04)	n	n
	Blood creatinine increased [a]	Common 100 (1.09)	**Y** 3 (0.03)	n	n
	Blood thyroid stimulating hormone increased [a]	Common 92 (1.00)	n	n	n
	Blood bilirubin increased	Uncommon 49 (0.53)	**Y** 4 (0.04)	n	n
Metabolism and Nutrition Disorders	Decreased appetite	Common 536 (5.82)	**Y** 5 (0.05)	n	n
	Hyponatremia	Uncommon 87 (0.94)	**Y** 17 (0.18)	n	n
Musculoskeletal and Connective Tissue Disorders	Musculoskeletal pain (including Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal discomfort, Myalgia, Neck pain, Pain in extremity, Pain in jaw)	Common 427 (4.64)	**Y** 4 (0.04)		
	Arthralgia (including Arthritis, Polyarthritis, and Osteoarthritis)	Common 400 (4.34)	**Y** 10 (0.11)		
	Myositis (including Polymyositis)[a]	Rare 6 (0.07)	**Y** 4 (0.04)		
	Polymyalgia rheumatica	Rare 6 (0.07)	**Y** [b] 1 (0.01)		
	Rhabdomyolysis [a, b]	Rare 1 (0.01)	**Y** 1 (0.01)		**Y** 1 (0.01)
Nervous System Disorders	Headache	Common 215 (2.33)	**Y** 4 (0.04)	n	n
	Neuropathy peripheral (including Burning sensation, Peripheral motor neuropathy, Polyneuropathy, Peripheral sensory neuropathy)	Common 102 (1.11)	**Y** 9 (0.10)	n	n
	Dizziness	Uncommon 83 (0.90)	**Y** 3 (0.03)	n	n
	Cranial nerve disorder [a]	Uncommo	**Y**	n	n

System Organ Class	Preferred Term	Overall Frequency N (%)	Serious ADRs N (%)	Life Threatening ADRs N (%)	Fatal ADRs N (%)
		n 12 (0.13)	6 (0.07)		
	Myasthenic syndrome (including Myasthenia gravis)	Rare 3 (0.03)	**Y** 3 (0.03)	n	n
	Guillain-Barre syndrome	Rare 2 (0.02)	**Y** 2 (0.02)	n	n
	Demyelination (including Demyelinating polyneuropathy)	Rare 2 (0.02)	**Y** 2 (0.02)	n	n
	Encephalitis including Autoimmune encephalitis)	Rare 2 (0.02)	**Y** 2 (0.02)	n	**Y** [b] 1 (0.01)
Renal and Urinary Disorders	Renal failure (including Acute kidney injury)	Uncommon 41 (0.45)	**Y** 24 (0.26)	**Y** 2 (0.02)	n
	Nephritis (including Autoimmune nephritis, Tubulointerstitial nephritis)	Uncommon 14 (0.15)	**Y** 11 (0.12)	n	n
Respiratory, Thoracic, and Mediastinal Disorders	Pneumonitis (including Interstitial lung disease, Organizing pneumonia)	Common 276 (3.00)	**Y** 152 (1.65)	**Y** 7 (0.08)	**Y** 9 (0.10)
	Dyspnea	Common 231 (2.51)	**Y** 35 (0.38)	**Y** 1 (0.01)	**Y** 3 (0.03)
	Cough	Common 222 (2.41)			
	Respiratory failure (including Respiratory distress) [a]	Uncommon 18 (0.20)	**Y** 16 (0.17)	**Y** 2 (0.02)	**Y** 7 (0.08)
	Lung infiltration	Rare 7 (0.08)	**Y** 2 (0.02)	n	n
Skin and Subcutaneous Tissue Disorders	Rash (including Rash maculo-papular, Rash generalized, Rash erythematous, Rash pruritic, Rash follicular, Rash macular, Rash papular, Rash pustular, Rash vesicular, Dermatitis, Dermatitis acneiform, Dermatitis allergic, Dermatitis exfoliative, and Drug eruption)	Very Common 1010 (10.96)	**Y** 20 (0.22)	n	n
	Pruritus (including Pruritus generalized)	Common 722 (7.84)	**Y** 2 (0.02)	n	n
	Dry skin	Common 182 (1.98)	n	n	n
	Vitiligo	Common 99 (1.07)	n		
	Erythema	Uncommon 75 (0.81)	n		
	Alopecia	Uncommon 60 (0.65)	n		

System Organ Class	Preferred Term	Overall Frequency N (%)	Serious ADRs N (%)	Life Threatening ADRs N (%)	Fatal ADRs N (%)
	Urticaria	Uncommon 40 (0.43)	n		
	Psoriasis	Uncommon 18 (0.20)	**Y** 3 (0.03)		
	Erythema multiforme	Rare 7 (0.08)	**Y** 3 (**0**.03)		
	Rosacea	Rare 2 (0.02)	n		
	Toxic epidermal necrolysis	Rare 1 (0.01)	**Y** 1 (0.01)		**Y** 1 (0.01)
Vascular Disorders	Hypotension [a]	Uncommon 43 (0.47)	**Y** 5 (0.05)	n	n
	Hypertension	Uncommon 42 (0.46)	n	n	n
	Vasculitis	Rare 2 (0.02)	n	n	n

[a] ADR not included in previous IB version 14.

[b] Despite single reported occurrence, this event is considered to be ADR based on observed nivolumab safety profile across treatment groups.

Appendix J Schedule of Procedures and Observations

Schedule of Procedures and Observations

Evaluation	Baseline[1]	Day -14	Each Cycle Day 1	Each Cycle Day 15	End of Cycle 1	Day 1 of Cycle 5 and every 4th cycle thereafter	End of Treatment	Follow-Up[2]
Medical History with Pre-existing Conditions	X[1]							
Physical Examination[4] and/or vital signs[5]	X[3]	X[4,5]	X[4,5]	X[5]		X[4,5]	X[4, 5]	
Hematology[6]	X	X	X[7]	X[7]		X	X	
Chemistry[8]	X	X	X[8]	X[8]		X	X	
Pregnancy Test (Urine)	X[1a]							
ECOG Performance Status	X	X	X				X	
HLA Typing	X[1b]							
IPSS/ IPSS-R (Appendix E and Appendix F)	X[20]					X	X	

Evaluation	Baseline[1]	Day -14	Each Cycle Day 1	Each Cycle Day 15	End of Cycle 1	Day 1 of Cycle 5 and every 4th cycle thereafter	End of Treatment	Follow-Up[2]
HIV, HBV, HBC	X[19]							
Response Assessment (Appendix D, Appendix E, Appendix F) and TTT						X	X	
Bone Marrow Aspirate and Biopsy[9]	X				X[18]	X	X[14]	X[21]
Endocrine Function Evaluation [17]: TSH	X				X			
Cardiac Safety Markers [15]	X[1a]				X			
Electrocardiogram [16]	X[1a]				X			
Echocardiogram [16a]	X[1a]							
Urinalysis	X[1a]				X	X		
Research Samples								
Correlative Blood Sampling	X[12]	X[12]	X[12]			X[12]	X[12]	X[12]
Bone Marrow Aspirate	X[13]				X[13]	X[13]	X[13,14]	X[13]
Study Drugs								
CDX-1401/ Poly-ICLC injection		X[10,11]		X[10, 11]		X[10,11]		
Decitabine			Day 1 *through* Day 5 of each treatment cycle[10 a]					
Nivolumab			Day 1 *and* Day 15 of each treatment cycle[10 b]					
Concomitant Medications	X[1]	X	X			X	X	X
Adverse Events		X	X	X	X	X	X	X
Survival Status								X

1 Performed within 4 weeks prior to first dose of CDX-1401/poly-ICLC) unless otherwise indicated.
1a: Performed within 3 week prior to first dose of CDX-1401/poly-ICLC) unless otherwise indicated
1b: Patients who do not require HLA typing for determination of transplant eligibility will have HLA typing sent for study purposes: Each site will perform their own HLA analysis according to institutional guidelines. **Samples taken at** RPCI: 1, 10 mL lavender-top tube to be sent to RPCI Immune Analysis Facility c/o Junko Matsuzaki, CCC room 416, x-8459).

2 Performed 30 days, 60 days, 90 days, and 180 days (± 3 days) following last dose of study drug (last immunization with CDX-1401/poly ICLC/nivolumab). Assessment may be collected via telephone if the patient elects to come off study and is no longer coming to clinic.

3 Height collected at baseline only.

4 Physical examination on day -14 and day 1 of each cycle (or up to 3 days prior to the beginning of a cycle) and at end of treatment

5 Vital signs including temperature, heart rate, oxygen saturation, respiratory rate, body weight and blood pressure prior to CDX-1401/poly ICLC dosing on day -14 and day 15 of each cycle (cycles 1-4) or day 1 of each 4th cycle (cycles 5+) and prior to decitabine dosing on day 1 of each cycle

6 CBC with manual differential

7 Once per week each cycle during cycles 1-4, from cycles 5 onward on Day 1 and as clinically indicated. Used to assess hematologic improvement per modified International Working Group criteria for MDS on Day 1 every cycle 1.

8 CMP, LDH, uric acid, amylase and, lipase. Once per week each cycle during cycles 1-4 and, on Day 1from cycle 5 and onward and, as clinically indicated.

9 Bone Marrow Aspirate and Biopsy, Flow Cytometry, Conventional Cytogenetics+/- FISH as appropriate. At the end of cycle 1 a Bone Marrow aspirate is to be done purely for collection of correlative specimens, unless the patient has demonstrated sufficient clinical response to warrant disease assessment at the discretion of the treating physician. **Note:** At the end of Cycle 1, if a bone marrow aspirate is not able to be done, a bone marrow biopsy may be performed instead Thereafter a complete bone marrow assessment to be done every 4th cycle (per standard of care) for response assessment. If bone marrow is unable to be obtained due to dry tap, collected 4 additional green top tubes of peripheral blood.

10 **CDX-1401/poly-ICLC** administered on day -14 of cycle 1 and then *day 15 of every cycle for the first 4 cycles*.
NOTE: After Cycle 4: to be given on *day 1 of every 4th cycle as a booster (i.e. on day 1 of cycles 8, 12, 16, 20, 24)*.
10a: Decitabine administered on days 1-5 of each cycle.
10b: Nivolumab administered every 2 weeks on days 1 and 15 of each cycle for the first 4 cycles.
Note: After Cycle 4: to be given on day 1 of every cycle 5 and above

11 Following administration of the CDX-1401/poly ICLC patients will be observed for 1 hour and undergo temperature, blood pressure and heart rate monitoring every 30 minutes.

12 Study blood work includes the following: At Baseline: Six green top tubes, 1 gold top tube; Cycle 1 day -14: 6 green top tubes, 1 gold top; Cycles 1-4 once weekly: 6 green top tubes; Cycles 5-end of study, every 2 weeks: 6 green tops and 1 gold top (see section 11.11.1). If it is determined that there is an inadequate cell number for cryopreservation and immunomonitoring, at any visit, sample acquisition may be repeated at the next scheduled blood draw.

13 Study Bone marrow samples for T-cell and methylation and gene expression studies, 4 green tops tubes to be obtained each time a bone marrow assessment is to be done (see Section 11.11.2).

14 End of study bone marrow may be done +/- 14 days from day 29 of the last cycle of decitabine for convenience.

15 Troponin-I, CK-MB, will be obtained at baseline (within 4 weeks prior to first dose of study drug) and at the end of Cycle 1 and as clinically indicated.

16 Electrocardiogram will be performed at baseline and at the end of Cycle 1 and as clinically indicated.

16^{a}: Echocardiogram will be performed at baseline or anytime as clinically indicated.

17 For **endocrine function monitoring**: Follow up- 6-8 weeks with repeat labs (may be done sooner if patient is symptomatic): refer to Endocrinology if abnormal labs. If patient is symptomatic, start initial treatment (most commonly thyroid replacement and/or hydrocortisone): always replace steroids first and thyroid hormone a few days later to prevent worsening of adrenal insufficiency. In cases of thyroiditis (low TSH, high free T4), treat symptomatically with beta-blockers and refer to Endocrinology. Note: Some patients with hypophysitis will require high dose steroids with taper and MRI pituitary. Refer to Appendix H for immune-related adverse event management guidelines.

18 At the end of cycle 1 a Bone Marrow aspirate is to be done purely for collection of correlative specimens (see Section 11.9.2) unless the patient has demonstrated sufficient clinical response to warrant disease assessment at the discretion of the treating physician. **Note:** At the end of Cycle 1, if a bone marrow aspirate is not able to be done, a bone marrow biopsy may be performed instead. Thereafter, a complete bone marrow assessment to be done every 4th cycle (per standard of care) for response assessment.

19 Testing for HIV I/II Ab, HBsAg, HCV Ab+/- PCR should be done only in patients for whom there is a concern for prior infection with one of these viral pathogens. Testing is NOT required if there is no history of infection.

20 Refer to Appendix E and Appendix F for calculation instructions.

21 Bone marrow biopsy per institutional guidelines for patients on study < 2 years. Bone marrow biopsy every 6 months (± 2 months) for patients on study for ≥ 2 years with correlative samples. Correlative samples to be collected at any time point when patient has a bone marrow biopsy for standard of care.

Appendix K Network Site Instructions

1. CONTACT INFORMATION

All questions related to the protocol or study implementation should be directed to:

Roswell Park Cancer Institute
CRS Network Office
ASB K 104
Buffalo, New York 14263
Telephone:
Monday - Friday; 8: 30 AM to 5: 00 PM EST
716-845-4169
After hours, weekends, and holidays request the RPCI Investigator
716-845-2300
Fax: 716-845-8743

2. INFORMED CONSENT

- Informed consent must be obtained by the **site Investigator/designee** from any participants wishing to participate, **prior to any procedures or treatment**.
- An informed consent template is provided by RPCI and can be amended to reflect institutional requirements.
- All consent changes **must** be reviewed by RPCI Network Office prior to submission to the site IRB.
- The informed consent must be IRB approved.
- Always check that the most up to date version of the IRB approved consent is being used.
- Within 5 business days, notify the RPCI Network Office of all participant withdrawals or consent to limited study participation and appropriately document the discontinuation and the reason(s) why.

3. PARTICIPANT REGISTRATION

The participant completes the Gender, Race, and Ethnicity Form and this is placed in the study binder.

RPCI does not grant exceptions to eligibility criteria.

Phase 1 Protocol Registration Instructions

Contact the RPCI Network Monitor to verify that a slot is available in the open cohort when a participant has been identified. **Do not have the participant sign consent prior to verifying an open slot.**

- After the participant signs consent, the Subject Screening and Enrollment Log must be faxed or emailed to the RPCI Network Monitor within 1 business day. The RPCI Network

Monitor will confirm receipt of the Subject Screening and Enrollment Log and email the participant ID number.

- When the participant has met eligibility, a signed eligibility checklist and other requested documentation will be faxed or emailed to the RPCI Network Monitor.
- Within 1 business day of receipt of the eligibility check list, the RPCI Network Monitor will fax or email the cohort assignment and dose level.
- An email must be sent by the site to confirm receipt of the cohort assignment and to provide the planned treatment start date.

4. STUDY DEVIATIONS

- If a deviation has occurred to eliminate hazard, this must be reported to the RPCI Network, site IRB and any other regulatory authority involved in the study.
- ALL study deviations will be recorded on the **Study Deviation Log**.
- Participants inadvertently enrolled with significant deviation(s) from the study-specified criteria will be removed from the study, at the discretion of the Principle Investigator.

5. STUDY DOCUMENTATION

- Study documents must be filled out completely and correctly. Ditto marks are not allowed.
- If an entry has been documented in error put a single line through the entry and initial and date the change. The RPCI Network Monitor must be able to read what has been deleted.
- Do **NOT** use white-out, magic marker, scratch-outs.
- Do **NOT** erase entries.
- Use only black ink for documentation on the accountability form and any other study forms.
- It is the responsibility of RPCI to inform the Investigator/ institution as to when these documents no longer need to be retained. If, for any reason, the Investigator desires to no longer maintain the study records, they may be transferred to another institution, another investigator, or to RPCI upon written agreement between the Investigator and RPCI.

6. DRUG ACCOUNTABILITY

Drug accountability must be strictly maintained.

- Responsibility rests solely with the Investigator but can be delegated as appropriate (e.g., to pharmacy personnel).
- A drug accountability record form (DARF) will record quantities of study drug received, dispensed to participants and wasted, lot number, date dispensed, participant ID number and initials, quantity returned, balance remaining, manufacturer, expiration date, and the initials of the person dispensing the medication.

- Study drug supply will only be used in accordance with the IRB approved study.
- Drug accountability forms are protocol and agent specific, they are study source documents and will be used to verify compliance with the study.
- An inventory count must be performed with each transaction. Any discrepancies shall be documented and explained.
- Drug accountability forms must be stored with study related documents.
- Each medication provided for this study and each dosage form and strength must have its own DARF.
- Dispensing the wrong study supply is considered a **medication error**.
- **NEVER** replace investigational agents with commercial product.
- Do **NOT** "transfer", "borrow" or "replace" supplies between studies.

7. SERIOUS ADVERSE EVENT REPORTING

The site Investigator or designated research personnel will report all SAEs, whether related or unrelated to the investigational agent(s) to the **IRB in accordance with their local institutional guidelines**. The site will notify the RPCI Network Monitor within 1 business day of being made aware of the SAE. In addition AEs must be reported to the drug supporters. See Section 17.4.1 of the protocol and Section 17.5 regarding additional notification requirements to BMS and Celldex. A preliminary written report must follow within 1 business day of the first notification using the following forms:

- MedWatch 3500A
- RPCI SAE Source Form

A complete follow-up report must be sent to the RPCI Network Monitor when new information becomes available.

- If this is a Phase 1 study the site Investigator or designated research personnel will complete and send the **Serious Adverse Event / Possible Dose Limiting Toxicity Memo** to notify the appropriate RPCI personnel of an SAE or potential DLT via email: Phase1DLTnetwork@Roswellpark.org.

8. UNANTICIPATED PROBLEM REPORTING

An unanticipated problem (UP) is any incident, experience, or outcome that meets all of the criteria in **Section 17.6**.

For all adverse events occurring that are unanticipated and related or possibly related to the research drug, biologic or intervention, the participating physician or delegated research staff from each site will notify their local **IRB in accordance with their local institutional guidelines**. The site must also notify the RPCI Network Monitor within 1 business day of being made aware of the Unanticipated Problem by completing the **RPCI Unanticipated Problem Report Form** and faxing or emailing it to the RPCI Network Monitor.

9. DATA AND SAFETY MONITORING

Weekly or bi-weekly teleconferences will be scheduled to review participant adverse events and study status. The site Investigator and study coordinator are expected to attend.