PARKER INSTITUTE
for CANCER IMMUNOTHERAPY

Protocol Title: A Multicenter, Open-Label, Exploratory Platform Study to Evaluate Biomarkers and Immunotherapy Combinations for the Treatment of Patients with Metastatic Castration-resistant Prostate Cancer

Appendix Cohort B

Protocol Number: PICI0033

Amendment Number: Not applicable

Compound Number: CDX-301, Poly-ICLC, Nivolumab

Short Title: Platform Study for Prostate Researching Translational Endpoints Correlated to Response to Inform Use of Novel Combinations (PORTER)

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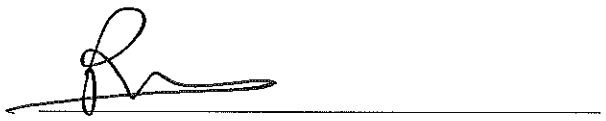

Date: 25 JAN 2019

Ramy Ibrahim, MD
Chief Medical Officer

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by Parker Institute for Cancer Immunotherapy.
- Not to implement any changes to the protocol without written agreement from Parker Institute for Cancer Immunotherapy and prior review and written approval from the Institutional Review Board or Independent Ethics Committee except where necessary to eliminate an immediate hazard to participants.
- That I am thoroughly familiar with the appropriate use of the study drug(s), as described in this cohort appendix and any other information provided by Parker Institute for Cancer Immunotherapy including, but not limited to, the current Investigator's Brochure(s).
- That I am aware of, and will comply with, the International Conference on Harmonisation for Good Clinical Practice (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the study drugs, the Parker Institute for Cancer Immunotherapy study protocol, and of their study-related duties and functions as described in the protocol.
- That I agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the Parker Institute for Cancer Immunotherapy or for a partnership in which the Parker Institute for Cancer Immunotherapy is involved, and that I will immediately disclose in writing to the Parker Institute for Cancer Immunotherapy if any person who is involved in the study is debarred, or if any proceeding for debarment is pending.

Signature: _____ Date: _____

Name (print): _____

Principal Investigator

Site Number: _____

Amendment(s) to Appendix Cohort B

Text revisions resulting from the amendment(s) are incorporated in the synopsis and body of the Appendix Cohort Amendment. Major changes to the appendix cohort are summarized below.

Key Revisions in Amendment 1 (24 January 2019)

Section # and Name	Description of Change
Study Design	
1.3 Schema, Figure 2	Modified to improve identification of key research procedure time points.
Study Intervention	
6.6.4 Dose Modifications for CDX-301	Added text to reinforce that doses of CDX-301 should be withheld (eg, skipped) for toxicity attributed to CDX-301. Add text to clarify that toxicities attributed to CDX-301 that require dose delays greater than 6 weeks will require Medical Monitor approval for the participant to restart treatment.
6.6.5 Dose Modifications for Poly-ICLC	Add text to clarify that toxicities attributed to poly-ICLC that require dose delays greater than 6 weeks will require Medical Monitor approval for the participant to restart treatment.
Clarification of Document	
General Revisions	Document updated to address minor typographical errors and editorial changes for clarity.
Appendix B-1	Reordered the management algorithms to match the order on the appendix cover page.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol Title:

A Multicenter, Open-Label, Exploratory Platform Study to Evaluate Biomarkers and Immunotherapy Combinations for the Treatment of Patients with Metastatic Castration-resistant Prostate Cancer

Appendix Cohort B

Short Title:

Platform Study for Prostate Researching Translational Endpoints Correlated to Response to Inform Use of Novel Combinations (PORTER)

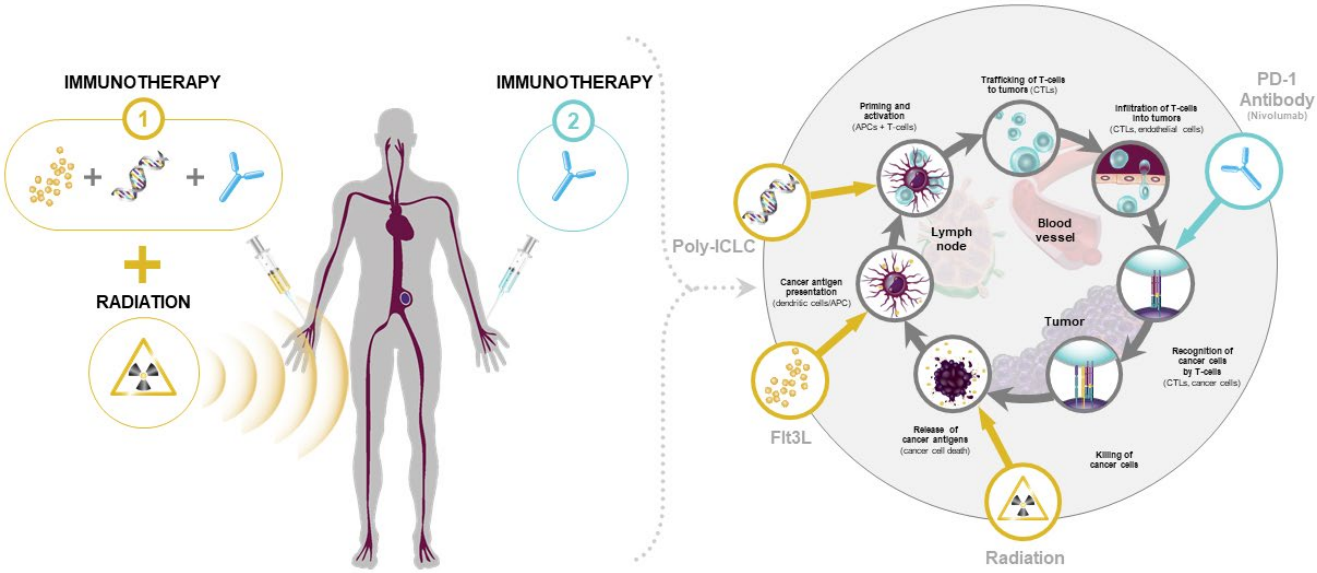
Note to Investigators: This cohort appendix is intended to supplement the core protocol, and as such, will focus on combination-specific (stereotactic body radiation therapy [SBRT], CDX-301, poly-ICLC [polyinosinic-polycytidylic acid stabilized with polylysine and carboxymethylcellulose], and nivolumab) information that is not already available in the core protocol.

Rationale:

This study cohort is designed to explore a multi-pronged approach to induce immunogenic cell death, mobilizing and activating dendritic cells (DCs), and overcoming adaptive immune resistance (T cells) in metastatic castration-resistant prostate cancer (mCRPC) (Figure 1). Immunogenic cell death induces the release of tumor antigens. Maturation and activation of DCs, an antigen presenting cell, mediates antigen presentation to CD8 T cells to stimulate antitumor immunity. Programmed cell death 1 (PD-1) blocking antibodies allow for the activation of tumoral CD8 T cells and the promotion of antitumor immunity. Specifically:

- Radiation therapy to induce immunogenic cell death of the tumor
- Flt3 ligand (CDX-301) to induce mobilization and activation of DCs
- Poly-ICLC and radiation therapy to induce maturation/activation of DCs
- Anti-PD-1 monoclonal antibody (nivolumab) to overcome immune suppression of tumoral T cells

Figure 1: Mechanism of Action for SBRT + CDX-301 + Poly-ICLC + Nivolumab



Objectives and Endpoints:

Refer to the core protocol.

Combination-specific exploratory objectives include:

Combination-specific Exploratory Objectives	Endpoints
• To evaluate the PK of CDX-301 and/or nivolumab. • To evaluate the immunogenicity (ADA) of CDX-301 and/or nivolumab.	• Sparse PK analysis. • Presence of ADA against CDX-301 and/or nivolumab.

ADA = anti-drug antibodies; PK = pharmacokinetics

Overall Design, Number of Participants, Follow-up, and Data Monitoring Committee:

Refer to the core protocol.

Intervention Groups and Duration:

Participants will be assigned to receive one of the enrolling immunotherapy combination study interventions. In this cohort, participants will receive SBRT, CDX-301, poly-ICLC, and nivolumab as follows:

Intervention	Dose	Frequency	Route	Schedule
CDX-301	75 µg/kg	QD	SC	Days 1 -5
SBRT	30-50 Gy in 1-5 doses. Radiation will start on Day 1 or 2			
Poly-ICLC	1 mg	Twice weekly x 3 weeks	IM	Starting on Day 1
Nivolumab	480 mg	Q4W	IV over 30 minutes	Starting Day 1

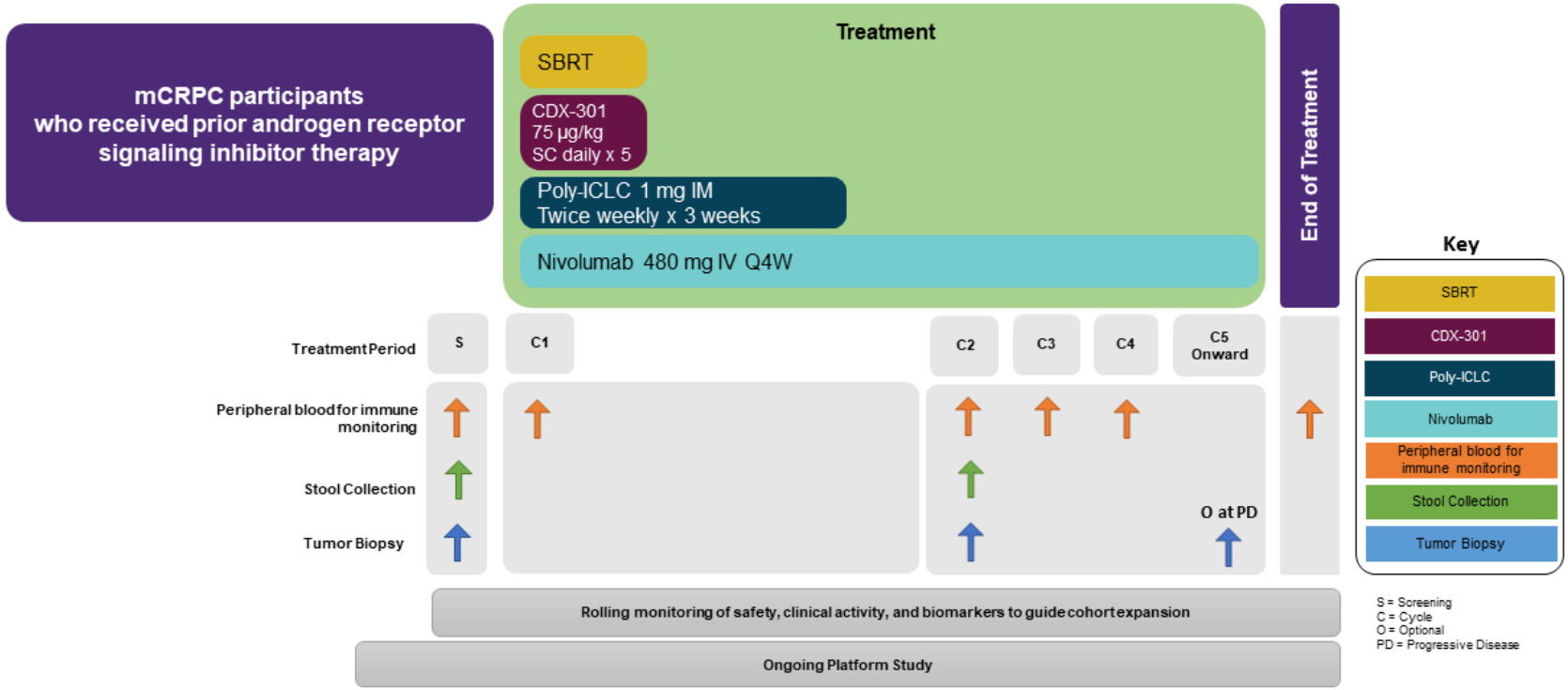
Gy = gray; IM = intramuscular(ly); IV = intravenous(ly); QD = daily; Q4W = every 4 weeks; SBRT = stereotactic body radiation therapy; SC = subcutaneous(ly)

SBRT and CDX-301/poly-ICLC will be administered during the first cycle only. Nivolumab will be administered for up to 2 years, unless the participant: is no longer clinically benefiting (as evidenced by symptomatic or radiographic disease progression and/or clinical deterioration); experiences any toxicity meeting specified discontinuation criteria (see Section 6.6) or unacceptable toxicity in the best clinical discretion of the treating physician (ie, Investigator discretion); reaches the maximum duration of study intervention; or withdraws consent. In this cohort, a cycle is defined as 4 calendar weeks.

1.2 SCHEMA

The study schema is depicted in Figure 2.

Figure 2: Study Schema



IM = intramuscularly; IV = intravenously; mCRPC = metastatic castration-resistant prostate cancer; Q4W = every 4 weeks; SBRT = stereotactic body radiation therapy; SC = subcutaneously

Note: The horizontal axis is not linearly scaled, so the interval for Cycle 1 appears to be much longer than for the subsequent cycles.

SBRT, CDX-301, and poly-ICLC will be administered during the first cycle only. Nivolumab will be administered for up to 2 years, unless the participant: is no longer clinically benefiting (as evidenced by symptomatic or radiographic disease progression and/or clinical deterioration); experiences any toxicity meeting specified discontinuation criteria (see Section 6.6) or unacceptable toxicity in the best clinical discretion of the treating physician; reaches the maximum duration of study intervention; or withdraws consent. A cycle is defined as 4 calendar weeks. Participants will be followed for up to 2.5 years from the time of the initiation of study intervention.

This study design is applicable to Stage 1, as well as Stage 2 if the cohort is expanded.

1.3 SCHEDULE OF ACTIVITIES

The Schedule of Activities (SOA) shown in Table 1 is specific for this combination and supersedes the SOA provided in the core protocol.

Table 1: Schedule of Activities

Tests & Procedures	Screening/ Enrollment[a]	On-Treatment: SBRT + CDX-301 + poly-ICLC + Nivolumab						End of Treatment[b]	Follow up	
		Cycle 1 (Q4W)				Cycles 2,3, and 4	Cycle 5 Onward			
Day	Day -28 to Day -1	Day 1	Day 2 - 5	Day 8	Day 15	Day 1	Day 1	14 - 28 days after last dose	110 days after last dose	Q3M[c]
Window (days)	-28			± 1	± 1	± 3	± 3	± 7	± 10	± 14
Informed consent[d]	X									
Review of I/E criteria	X									
Medical/cancer history	X									
Physical examination	X	X				X	X	X		
ECOG performance status	X	X				X	X	X	X	
Vital signs (See Core Protocol Section 8.2.3)	X	X				X	X	X		
Body weight	X	X		X	X	X	X (Cycles 5, 8, 11, 14, 17, 20, 23, and 26)	X		
Hematology (see Table 10)	X	X[e]		X[e]	X[e]	X[e]	X[e]	X	X	
Clinical chemistry (see Table 10)	X	X[e]		X[e]	X[e]	X[e]	X[e]	X	X	
Urinalysis	X							X		
Prostate-specific antigen	X	X				X	X	X	X	
Testosterone level	X									
12-lead ECG	X					X (Cycles 2 and 4)				
Circulating tumor cells[f]		X[e]				X[e]	X[e]	X		
cfDNA (blood)[g]	X					X[e] (Cycles 2 and 4)		X		

Tests & Procedures	Screening/ Enrollment[a]	On-Treatment: SBRT + CDX-301 + poly-ICLC + Nivolumab						End of Treatment[b]	Follow up	
		Cycle 1 (Q4W)				Cycles 2,3, and 4	Cycle 5 Onward			
Day	Day -28 to Day -1	Day 1	Day 2 - 5	Day 8	Day 15	Day 1	Day 1	14 - 28 days after last dose	110 days after last dose	Q3M[c]
Window (days)	-28			± 1	± 1	± 3	± 3	± 7	± 10	± 14
Circulating soluble analytes/PK/ADA[h]	X	X[e]	X[e] (Day 5)	X[e]	X[e]	X[e] (Cycles 2, 3, and 4)		X	X	
Blood immune biomarkers[h]	X	X[e]	X[e] (Day 5)	X	X	X[e] (Cycles 2, 3, and 4)		X		
Archival tumor tissue	X									
Tumor biopsy[i]	X					X (Cycle 2)		X (at PD [optional])[i]		
Stool collection[j]	X					X (Cycle 2)[j]				
Concomitant medications	X	X	X	X	X	X	X	X	X	
Adverse events	All AEs and SAEs will be collected for at least 100 days after the last dose of study intervention[k]									
Radiation therapy[l]		X	X							
CDX-301 administration[m]		X	X							
Poly-ICLC administration[n]		X	X (twice weekly[n])	X (twice weekly[n])	X (twice weekly[n])					
Nivolumab administration[o]		X				X	X			
Radiographic disease assessment	X	At Week 8 (± 1 week), repeat every 8 weeks (± 1 week) for the first 24 weeks, and every 12 weeks (± 1 week) thereafter until radiographic PD or start of subsequent therapy								
Review of alternate anticancer therapy[p]									X	X
Follow up for overall survival									X	X

ADA = anti-drug antibodies; AE(s) = adverse event(s); cfDNA = cell-free deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; Gy = grays; I/E = inclusion/exclusion; IM = intramuscularly; IV = intravenously; PD = progressive disease; PK = pharmacokinetics; Q3M = every 3 months; Q4W = every 4 weeks; QD = every day; SAE(s) = serious adverse event(s); SC = subcutaneously

[a] Tests/procedures performed as standard of care prior to obtaining informed consent and within 28 days prior to the first dose of study intervention do not have to be repeated at screening.

[b] The End of Treatment Visit will be completed following the last dose of study intervention, either at the completion of the on-treatment phase or at early discontinuation.

[c] For up to 2.5 years from the initiation of study intervention, participants in the follow up phase will be contacted by the site to collect alternate anticancer therapy information and determine survival status.

[d] Informed consent must be obtained prior to any study-specific procedures and may be obtained prior to the 28-day screening window.

[e] Blood samples should be collected prior to administration of any study intervention.

[f] Circulating tumor cells will be collected at baseline (ie, Day 1 of Cycle 1 prior to study intervention administration), Day 1 of each cycle (prior to study intervention administration), and EOT.

[g] cfDNA (blood) will be collected at baseline (ie, screening visit prior to study intervention administration), Day 1 of Cycle 2 and Cycle 4, and EOT.

[h] Circulating soluble analytes, PK and ADA blood sample, and/or blood immune biomarkers may be assessed at baseline (ie, screening and/or Day 1 of Cycle 1 prior to study intervention administration), prior to study intervention administration on Days 1, 5, 8, and 15 of Cycle 1 and Day 1 of Cycles 2-4, and at EOT and the first follow up visit.

[i] Participants will undergo 2-3 tumor biopsies: prior to beginning protocol therapy (ie, baseline biopsy, mandatory for all participants, including those with bone only disease if medically feasible), and during treatment (ie, on-treatment biopsy during Cycle 2, if medically feasible). On- treatment biopsy should occur as early as possible after the second dose (Day 2 – Day 10 of Cycle 2); however, any on treatment biopsy after Day 1 of Cycle 2 will be accepted. An optional biopsy may be obtained at the time of disease progression, including from participants who respond and subsequently progress. Every attempt should be made for the on-treatment biopsies to be taken from the same lesion as the pre-treatment biopsy when feasible.

[j] Stool will be collected at screening and during Cycle 2, if possible. Otherwise, any on-treatment stool sample will be acceptable. The stool sample may be collected at the clinic or at the participant's home.

[k] All SAEs will be collected from the time the participant signs informed consent. Prior to initiation of study intervention, only SAEs that are related to a protocol-mandated intervention, including those that occur prior to the assignment of study procedures should be reported. All AEs will be collected from the start of study intervention. All AEs and SAEs will be collected for at least 100 days after the last dose of study intervention. Refer to Section 8.3 of the core protocol for details regarding safety reporting for this study.

[l] Radiation therapy will be administered at 30 – 50 Gy in 1 – 5 doses, starting on Day 1 or 2.

[m] CDX-301 will be administered at a dose of 75 µg/kg SC QD x 5 days (Days 1 – 5 [ie, Monday – Friday]), concurrent with SBRT.

[n] Poly-ICLC will be administered at a dose of 1 mg IM twice weekly, at least 2 days apart, for 3 weeks starting on Day 1. The dose may be administered at any time of the day but should occur at approximately the same time on poly-ICLC administration days.

[o] Nivolumab will be administered at a dose of 480 mg IV over 30 minutes Q4W starting on Day 1 of Cycle 1 and will continue for up to 2 years, unless the participant: is no longer clinically benefiting (as evidenced by symptomatic or radiographic disease progression and/or clinical deterioration); experiences any toxicity meeting specified discontinuation criteria (see Section 6.6) or unacceptable toxicity in the best clinical discretion of the treating physician; reaches the maximum duration of study intervention; or withdraws consent. A cycle is defined as 4 calendar weeks. The time between nivolumab doses must not be less than 24 days.

[p] Collection of information related to any post-study intervention alternate anticancer therapy.

2 INTRODUCTION

Refer to the core protocol.

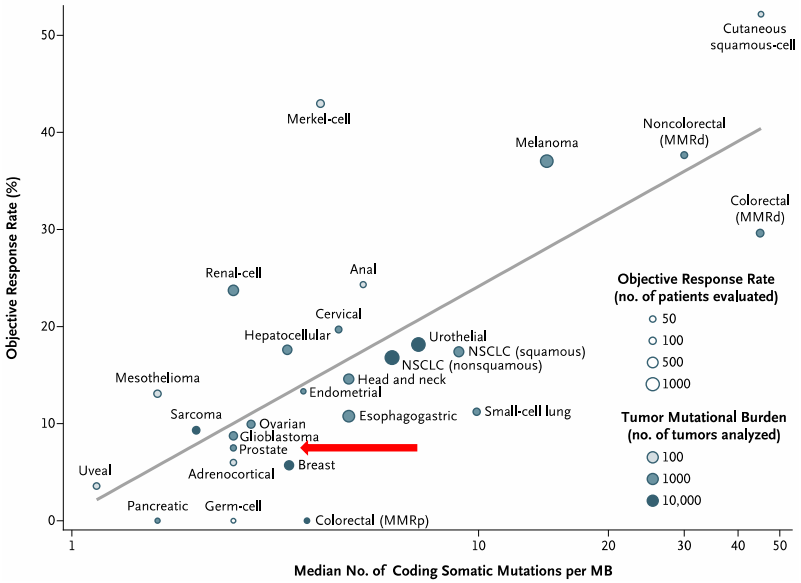
2.1 STUDY RATIONALE

Refer to the core protocol.

2.2 BACKGROUND

Immune checkpoint blockade, particularly with programmed cell death 1 (PD-1) or programmed cell death ligand 1 (PD-L1) antibodies, has changed the landscape for the treatment of a variety of advanced solid tumors. Though the majority of patients with a specific tumor type don't respond to treatment, a notable subset of patients across tumor types achieve durable responses in the context of relatively well tolerated therapy leading to the substantial enthusiasm for this therapeutic class (Figure 3). However, not only is there intra-tumor-type variability in the likelihood of response to PD-1/PD-L1 blockade but there is also substantial inter-tumor type heterogeneity (Yarchoan et al., 2017). Prostate cancer has been among the tumor types for which single-agent PD-1/PD-L1 blockade has been associated with relatively rare responses, and the responses that do occur are typically in the context of a genomically-defined subset of cancers (ie, mismatch repair deficient tumors) (Graff et al; 2016). Therefore, there is a critical need to develop rational combination strategies to extend the benefits of PD-1/PD-L1 blockade to patients with metastatic castration-resistant prostate cancer (mCRPC).

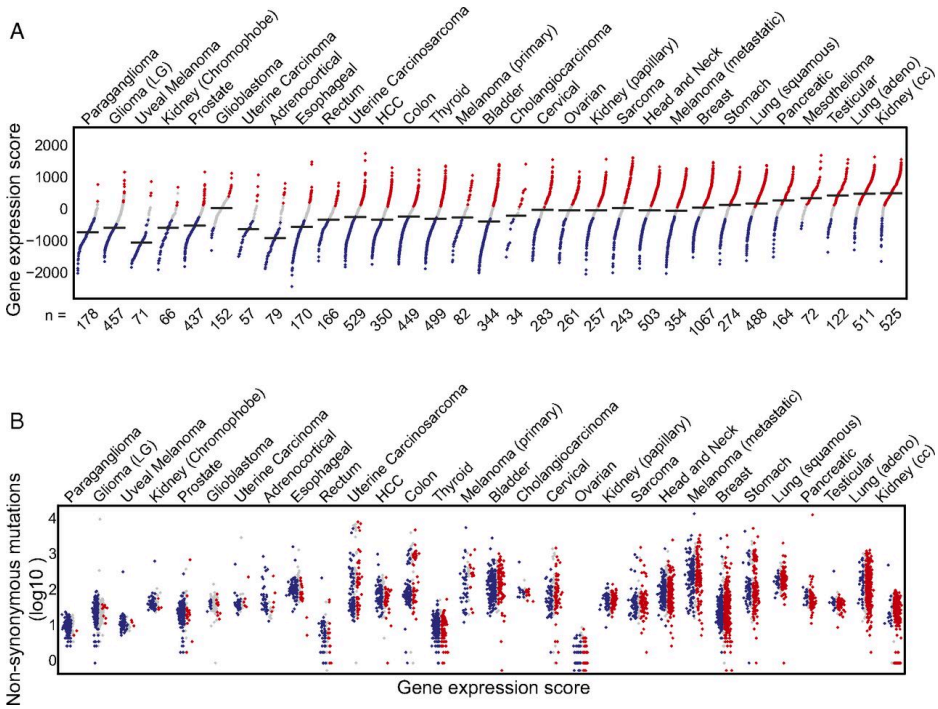
Figure 3: Correlation Between Tumor Mutational Burden and Objective Response Rate with Anti-PD-1 or Anti-PD-L1 Therapy in 27 Tumor Types



Source: Adapted from Yarchoan et al., 2017

Clues as to why prostate cancers may be less responsive to single-agent PD-1/PD-L1 blockade may be derived from studies exploring biomarkers predictive of response and resistance to treatment in tumor types associated with a higher likelihood of response. Indeed, multiple studies have demonstrated that patients with tumors harboring a higher tumor mutational burden (TMB) and/or with a pre-existing infiltration of T cells (or other measures of "hot" tumors) are more likely to respond to PD-1/PD-L1 blockade (Yarchoan et al., 2017; Tumeh et al., 2014). Interestingly, these two general categories of biomarkers have been shown to confer independent predictive/prognostic information in prior analyses such that patients with low TMB but high T cell infiltration have a similar likelihood of response compared with patients with high TMB but low T cell infiltration (Galsky et al., 2017). These observations may be extended to the heterogeneity in responses to PD-1/PD-L1 blockade across different tumor types; for example, renal cancer, despite generally harboring a relatively low TMB is frequently associated with high T cell infiltration and is felt to be a PD-1/PD-L1 treatment responsive tumor type. Prostate cancer, on the other hand, is generally associated with both a low TMB and low T cell infiltration (Figure 4).

Figure 4: Spectrum of Inflamed Tumor Microenviroment Phenotype and Tumor Mutational Burden Across Human Cancer Types



(A) the "inflamed" tumor microenvironment phenotype and (B) tumor mutational burden across human cancer types (Source: Spranger et al., 2016).

Consistent with observations from other groups, Spranger et al. reported a lack of correlation between measures of T cell infiltration and TMB across various tumor types (Figure 4; Spranger et al., 2016). This critical observation indicates that the lack of spontaneous immune infiltration in solid tumors is unlikely to be due simply to a lack of immunogenic tumor antigens. Rather, Spranger et al. demonstrated that tumors lacking T cell infiltration were also lacking in transcriptional profiles indicating the presence of dendritic cells (DCs). Together, these findings suggest that (a) strategies to restore T-cell entry into non-inflamed tumors should be developed to further improve outcomes with PD-1/PD-L1 blockade and (b) recruitment of DCs, key to the development of an adaptive immune response, may be a rate limiting step in the development of an inflamed tumor regardless of TMB, and furthermore, an immune response may be activated if this is combined with agents that induce immunogenic cell death.

2.2.1 Background on Radiation Therapy

External beam radiotherapy induces immunogenic cell death (Obeid et al., 2007) and production of maturation signals for DCs leading to improved cross presentation (Rovere et al., 1998; Golden et al., 2014) which are likely mechanisms for recurrently observed 'abscopal effects,' in which local radiotherapy causes regression of metastatic cancer at a distant site by itself or in combination with immune checkpoint blockade (Postow et al., 2012; Golden et al., 2013). The rationale behind combining with immunotherapy is to co-localize the immunogenic cell death and antigen release induced by radiation with effective antigen presenting cell (APC) processing and cross-presentation to cytotoxic T-cells (Gulley et al., 2005).

Given the potentially complimentary mechanisms of action of radiation therapy and immune checkpoint blockade, and the potential for therapeutic synergy, several studies have explored combination regimens. Indeed, in the randomized trial of ipilimumab versus placebo in patients with mCRPC progressing despite docetaxel, patients received one fraction of bone-directed radiotherapy (8 grays [Gy]) prior to ipilimumab versus placebo (Kwon et al., 2014). Unfortunately, this study failed to demonstrate a survival benefit with ipilimumab though this outcome may have been attributed to a variety of factors including the patient population, use of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blockade, and/or dose of radiation therapy.

Luke et al. recently reported the results of a large phase 1 study for patients with metastatic solid tumors progressing despite standard treatment (Luke et al., 2018). The primary aim was to evaluate the safety of pembrolizumab given in combination with multi-organ site ablative stereotactic body radiation therapy (SBRT). Two to four metastases were chosen for each patient and not all sites of disease were targeted with SBRT. Metastases > 65 cubic centimeters were partially irradiated. Pembrolizumab was initiated within 7 days after the final SBRT treatment. Among 73 patients included and treated with SBRT and at least 1 cycle of pembrolizumab, the

vast majority (94.5%) had two lesions treated with SBRT. Response Evaluation Criteria in Solid Tumors (RECIST) overall objective response rate was 13.5% in the 68 patients with imaging follow-up. Superior control of irradiated lesions was observed compared to non-irradiated target lesions for the 52 patients with paired data (p = 0.0005) with a mean percent tumor burden change -21.7% (standard deviation [SD] 24.3%) for irradiated lesions vs. 1.7% (SD 46.3%) for non-irradiated lesions (p = 0.0008). While abscopal response defined by 30% reduction in any single non-irradiated measurable lesion was present in 26.9% of patients, abscopal response was 13.2% when defined by 30% reduction in aggregate diameter of non-irradiated measurable lesions. Treatment was generally well tolerated with acceptable toxicity. Expression of interferon (IFN)-γ–associated genes from post–SBRT tumor biopsy specimens significantly correlated with nonirradiated tumor response. These findings provide rationale for further studies of combination SBRT plus PD-1 blockade.

The safety of SBRT has been demonstrated in the treatment of adrenal metastases, in which SBRT was associated with excellent local control and very low toxicity rates, providing an alternative to image-guided ablative procedures (Toesca et al., 2018). Furthermore, the analysis suggested that adrenal SBRT has minimal, if any, significant impact on renal function. Further studies with a larger patient population are needed to confirm these findings.

The acute toxicities associated with the use of SBRT in patients with localized prostate cancer have been primarily genitourinary (GU) and gastrointestinal (GI) in nature (Syed et al., 2017; Haque et al., 2017; King et al., 2013). In most studies, acute toxicities were limited to Grade 1 or 2; the incidence of ≥ Grade 3 toxicities was typically < 5%. While most late toxicities were Grade 1 or 2, the majority of studies have reported at least 1 ≥ Grade 3 late urinary toxicity (Syed et al., 2017).

2.2.2 Background on rhuFLT3L/CDX-301 (Celldex Therapeutics, Inc.)

rhuFLT3L/CDX-301 is the soluble recombinant human (rhu) protein form of the FMS-related tyrosine kinase 3 ligand (Flt3L), a hematopoietic cytokine. CDX-301 represents the 153 N-terminal amino acids of the human Flt3L extracellular domain after the cleavage of the N-terminal signal peptide.

Flt3L is a hematopoietic growth factor that plays an important role in the mobilization and expansion of stem cells and progenitors (Lyman and Jacobsen, 1998). In particular, it has been shown to facilitate the differentiation of both DCs and natural killer cells from hematopoietic stem cell precursors (Blom et al., 2000; Chen et al., 2005; Gilliet et al., 2002; Miller et al., 1999). Specifically, Flt3L directly induces the differentiation of a proportion of $CD34^{+}$ CD45RA- early progenitor cells into pre-DCs, and results in increased numbers of activated DCs (Blom et al., 2000; Breton et al., 2016). In healthy human volunteers it has been demonstrated that Flt3L

administration increases the number of DCs, as well as $CD14^+$ monocytes (Chen et al., 2005; Anandasabapathy et al., 2015; Maraskovsky et al., 1996; Pulendran et al., 1997).

Numerous pre-clinical models have shown the ability of Flt3L administration to mobilize a range of immune cell subsets, DCs predominant among these (Brasel et al., 1996; Fernandez et al., 1998; Kutzler and Weiner, 2004; Miller et al., 2003). Flt3L administration has demonstrated antitumor activity in a variety of tumor models including melanoma, lymphoma, leukemia, breast, colon, prostate, lung and hepatocellular carcinoma (Averbook et al., 2002; Ciavarra et al., 2000; Drexler et al., 1999; Esche et al., 1998; Hou et al., 2007; Wang et al., 2000; Chakravarty et al., 1999). Several preclinical studies have suggested combining Flt3L with radiation, checkpoint inhibitors, and/or poly-ICLC (polyinosinic-polycytidylic acid stabilized with polylysine and carboxymethylcellulose) results in significant antitumor activity and the ability to elicit an antitumor immune response in cold or resistant tumors. Preclinical studies have demonstrated improved antitumor effects and tumor-specific immunity when Flt3L is combined with radiotherapy. In a breast adenocarcinoma model, radiotherapy alone led to growth delay only in the irradiated tumors, whereas growth of distant (non-irradiated) tumors was also impaired by the combination of radiotherapy and Flt3L. Importantly, in this breast cancer adenocarcinoma model, Flt3L alone had no effect without radiotherapy and systemic tumor-specific immunity, known as the abscopal effect, was elicited by the combined therapy and shown to be T-cell mediated (Demaria et al., 2004). Additionally, radiotherapy plus Flt3L administration (500 µg/kg/day) over 10 days reduced pulmonary metastases in a murine model of Lewis lung carcinoma, retarded the growth of established tumors, induced tumor-specific T- cell immunity and significantly improved survival in C57BI/6 mice with established footpad tumors (Chakravarty et al., 1999). Preclinical models have also shown that Flt3L administration can enhance the antitumor immunity of checkpoint inhibitors such as PD-1 and CTLA-4 antibodies to promote tumor regression of non-immunogenic tumors (Lynch et al., 1997). When Flt3L is administered with poly-ICLC, a TLR3 agonist, it results in a marked increase in activated intratumoral DCs and renders resistant tumors susceptible to PD-1 blockage in mouse tumor models (Salmon et al., 2016).

Flt3L has been used in many early phase human clinical trials of different immunotherapeutic approaches—as an adjuvant or in order to mobilize DCs for collection to produce a cellular vaccine—in patients with colorectal cancer, non-small cell lung cancer, mesothelioma, and prostate cancer, among others, and demonstrated safety with minimal toxicity from Flt3L administration through multiple routes of administration (Fong et al., 2001; Freedman et al., 2003; Higano et al., 2004; Morse et al., 2000).

A study in 31 patients with nonmetastatic castration-resistant prostate cancer (nmCRPC) evaluated the impact of Flt3L administration on peripheral blood DCs and post-treatment

changes in prostate-specific antigen (PSA; Higano et al., 2004). DCs increased markedly from baseline to Day 15, and the increase was consistently observed after administration of Flt3L in each cycle. Mean percentages of DCs in peripheral blood ranged from 1.4% to 1.9% pre-cycle and from 10.1% to 13.9% on Day 15, and after the first cycle, absolute counts on Day 15 were approximately 29-fold higher than pre-cycle levels. Natural killer (NK) cell counts (CD56+) were found to be elevated after cycle 1 (154% increase versus 2.8% decrease in placebo group at Day 22). The most frequently experienced toxicity was injection site reaction, followed by asthenia, rash, and diarrhea. Although median PSA levels did not vary during any cycle, a significant slowing in velocity of PSA was observed while patients were on-study (relative velocity = 0.002) compared with prestudy PSA velocity (relative velocity = 0.007). Given that Flt3L consistently produced an increase in DC numbers and the slowing of PSA velocity after administration, the authors concluded that Flt3L warrants further study for the immunotherapy of prostate cancer.

Preliminary results of a single-arm study exploring CDX-301 plus SBRT for non-small cell lung cancer (NSCLC) were reported at the American Association for Cancer Research 2018 Annual Meeting (Ohri et al., 2018). In this study, SBRT was administered to a single lung lesion in 1-5 fractions concurrently with CDX-301 (75 µg/kg subcutaneously [SC] daily x 5). Among 9 patients enrolled at the time of the presentation, 7 had previously been treated with PD-1/PD-L1 blockade. Intriguingly, partial responses (excluding the irradiated lesion) were seen in 3/9 patients. Further, the regimen was demonstrated to be safe with no unexpected toxicities.

Refer to the Investigator's Brochure (IB; CDX-301/Recombinant Human Flt3 Ligand [rhuFlt3L] Investigator's Brochure, 2018) for detailed background information on rhuFLT3L/CDX-301.

2.2.3 Background on Poly-ICLC (Oncovir, Inc.)

Poly-ICLC (also known as Hiltonol®), is a stabilized double-stranded ribonucleic acid (dsRNA) 'host-targeted' therapeutic viral-mimic that exhibits broad innate and adaptive immune enhancing effects. It was used as an interferon inducer at high doses (up to 300 µg/kg intravenously [IV]) in cancer trials; at lower doses (10 to 50 µg/kg) it achieves a broader host defense stimulation, a potent adjuvant effect, anti-proliferative and antiviral effects (Maluish et al., 1985).

The possible antitumor and antiviral activity of poly-ICLC is thought to be dependent on its stimulation of at least 4 interrelated systems that may work independently or in concert with one another. These include the induction of IFN, the modulation of gene expression, a direct antiviral/antineoplastic effect, and a broad immune-enhancing effect.

While initially developed as an IFN inducer, poly-ICLC also has much broader biological effects in humans, including specific antiviral and antitumor actions. It is, more accurately, a synthetic,

stabilized dsRNA therapeutic viral mimic or pathogen associated molecular pattern 'danger signal' that activates multiple elements of innate and adaptive immunity, including induction of interferons, cytokines, and chemokines, NK cells, T-cells, myeloid DCs via the TLR3 and MDA5, RIG-I, 2'5'oligoadenylate synthetase (OAS), the P68 protein kinase (PKR), and other dsRNA-dependent host defense systems. In the current study, we seek to specifically exploit the ability of poly-ICLC to induce maturation of DCs (Longhi et al., 2009) for tumor antigen presentation. However, it is possible that the other immunomodulatory effects of poly-ICLC will also result in enhanced antitumor effects with the other components of the treatment protocol.

Poly-ICLC has a well-established history of use in the setting of clinical trials evaluating both its safety and efficacy in various malignancies. To date, over 85 clinical trials utilizing poly-ICLC have been registered at the clinicaltrials.gov website, dating back to a 1996 phase 1/2 trial of poly-ICLC for use in malignant gliomas.

Refer to the IB (Poly-ICLC Investigator's Brochure, 2018) for detailed background information on poly-ICLC.

2.2.4 Background on Nivolumab (Bristol-Myers Squibb Company)

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response. Opdivo® (nivolumab) is approved in the United States (US) for the treatment of several cancer types, including unresectable or metastatic melanoma (as monotherapy or in combination with ipilimumab) and as monotherapy in previously-treated metastatic NSCLC, advanced renal cell carcinoma (RCC), relapsed or refractory classical Hodgkin lymphoma (cHL), locally advanced or metastatic urothelial carcinoma (UC), recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN), microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC), and hepatocellular carcinoma (HCC). In phase 1 investigation, nivolumab did not demonstrate clinical activity in 17 participants with mCRPC. This is consistent with mCRPC having a low level of immune cell infiltrate and TMB. Treatment strategies to increase antigen presentation and immune infiltration and activation may improve the immune responsiveness of mCRPC to nivolumab.

Refer to the IB (Nivolumab Investigator's Brochure, 2018) and approved US prescribing information (Opdivo [nivolumab] US Prescribing Information [USPI], 2018) for detailed background information on nivolumab.

2.2.5 Rationale for SBRT + CDX-301+ Poly-ICLC+ Nivolumab Immunotherapy Combination

This study cohort is designed to explore a multi-pronged approach to overcome the low T cell infiltrate and TMB by promoting antitumor immunity in mCRPC by inducing immunogenic cell death, mobilizing and activating DCs to increase tumor antigen presentation and overcoming adaptive immune resistance in mCRPC (Figure 1). Specifically:

- Radiation therapy to induce immunogenic cell death of the tumor
- Flt3 ligand (CDX-301) to induce mobilization and activation of DCs
- Poly-ICLC and radiation therapy to induce maturation/activation of DCs, antigen presenting cells that mediate tumor antigen presentation to the CD8 T cells to stimulate antitumor immunity
- Anti-PD-1 monoclonal antibody (nivolumab) to overcome immune suppression of tumoral T cells

Data derived from preclinical studies support this combination approach. Salmon and colleagues, in mouse melanoma models, demonstrated that a specific subset of DCs, CD103+ DCs, were the only APCs transporting intact antigens to lymph nodes and priming tumor-specific CD8+ T cells (Salmon et al., 2016). CD103+ DCs were required to promote antitumoral effects upon blockade of the checkpoint ligand PD-L1; however, PD-L1 inhibition only led to partial responses. Systemic administration of the growth factor Flt3L plus poly I:C expanded and activated CD103+ DC progenitors in the tumor, enhancing responses to PD-L1 blockade and protecting mice from tumor rechallenge. Thus, similar to the in silico work described from Spranger and colleagues (Spranger et al., 2016), the paucity of activated CD103+ DCs in tumors was shown in this model by Salmon et al. to limit immune checkpoint blockade efficacy and combined Flt3L and poly I:C therapy was shown to enhance tumor responses to immune checkpoint blockade.

Further, data from clinical studies support this combination approach. The combinations of SBRT and anti-PD-1 therapy and SBRT and CDX-301 have been studied and/or are being assessed in ongoing studies in a number of tumor types, including NSCLC (Table 2). Results demonstrate that both combinations are well tolerated, with evidence of abscopal responses. Similarly, CDX-301 and poly-ICLC, in combination with CDX-1401 vaccine, have been studied in patients with melanoma (Table 2). Results of the study demonstrated that subjects receiving CDX-301 pretreatment showed substantial increases in DC, monocytes, and NK cells. Further, subjects receiving CDX-301 developed higher anti-vaccine antibody titers than those who did not receive CDX-301. The authors concluded that DC mobilization with Flt3L is safe and may enhance responses to DC-targeted vaccines (Bhardwaj et al., 2016). A study of nivolumab and poly-ICLC, in combination with CDX-1401 vaccine and decitabine, is ongoing.

Table 2: Clinical Studies Supporting the Co-administration of Components of this Study Intervention

Study	Disease Site	N	Combination	Findings
SBRT + Anti-PD-1 Combinations				
NCT02608385	Advanced Cancer	79	SBRT + anti-PD-1	Single arm study demonstrated treatment was well tolerated, with no radiation dose reductions. The overall ORR was 13.2% in the 68 patients with imaging follow-up. When defined as a 30.0% reduction in any single nonirradiated measurable lesion, the abscopal response was present in 26.9% of patients. Six dose-limiting toxicities defined as ≥ Grade 3, related to treatment. (Luke et al., 2018)
NCT02492568	NSCLC	64	SBRT + anti-PD-1	Randomized study (SBRT + anti-PD-1 vs anti-PD-1 therapy alone) demonstrated combination was well-tolerated and a promising strategy to augment the antitumor immune response with checkpoint blockade. ORR at 12 weeks was 41% vs 19%, respectively. Toxicity ≥ Grade 3 was experienced in 17% vs 22%, respectively. (Theelen et al., 2018)
NCT02684253	SCCHN	53	SBRT + anti-PD-1	Randomized study (SBRT + anti-PD-1 vs anti-PD-1 therapy alone) demonstrated combination was safe, but addition of SBRT to anti-PD-1 therapy failed to improve ORR (22.2% vs. 26.9%, respectively) or 1-year OS (53% vs 64%, respectively) in subjects with SCCHN. Treatment-related ≥ Grade 3 toxicities occurred in 11% vs. 15% of patients, respectively. (McBride et al., 2018)
NCT02826564	Urothelial Cancer	23	SBRT + anti-PD-1	Study ongoing to assess 2 groups of 10 patients each in phase 1, with an additional expansion of 13 patients in phase 2, to assess the safety and response rate of 2 different sequences of SBRT and anti-PD-1 therapy (SBRT prior to C1 vs prior to C3 of anti-PD-1 therapy). (Sundahl et al., 2017)
NCT02648282	Pancreatic Cancer	54	SBRT + anti-PD-1 + GVAX	Single arm, open-label study ongoing to assess distant metastasis free survival, OS, surgical resectability, pathologic response, QoL, and toxicity. (Lee et al., 2017)
SBRT + CDX-301 Combinations				
NCT02839265	NSCLC	9	SBRT + CDX-301	Single arm study yielded promising early results, with frequent abscopal effects and a high 4-month PFS (PFS4) rate. PR of lesions not targeted with SBRT ("abscopal effect") was observed in 5/9 subjects. PFS4 was achieved in 5/9 subjects overall. PR and PFS4 were achieved in 5/7 subjects who were previously treated with immunotherapy and in 0/2 subjects who were not previously treated with immunotherapy. No dose-limiting toxicities were observed. (Ohri et al., 2018)

CDX-301 + Poly-ICLC Combinations				
NCT01976585	Non-Hodgkin Lymphoma	30	CDX-301 + Poly-ICLC + low dose XRT	Study ongoing to assess 2 cohorts of 15 patients each with either previously untreated or relapsed/refractory iNHL to test the hypothesis that in situ vaccination will induce clinical remissions at distant (untreated) tumor sites. Data from this trial suggest that non-responders have larger populations of exhausted T cells. The addition of PD-1 reverses this exhaustion in mice, and results in significantly improved tumor regression. (Marron et al., 2015; Marron et al., 2017)
NCT02129075	Melanoma	60	CDX-1401 vaccine + Poly-ICLC ± CDX-301	Randomized study (CDX-301 + CDX-1401+ poly-ICLC vs CDX-1401+ poly-ICLC) demonstrated DC mobilization with Flt3L is safe and may enhance responses to DC-targeted vaccines. Preliminary analyses showed substantial (between ~15- to ~200-fold) increases of PBMC innate immune cells (DC, monocytes and NK cells) in subjects with CDX-301 pretreatment vs subjects without CDX-301. Further, there was development of higher anti-NY-ESO-1 antibody titers in subjects with CDX-301 pretreatment vs subjects without CDX-301. (Bhardwaj et al., 2016)
Anti-PD-1 + Poly-ICLC Combinations				
NCT03358719	Myelodysplastic Syndrome or AML	18	CDX-1401 vaccine + Poly-ICLC + Decitabine + Anti-PD-1	Single arm, open-label study ongoing to assess safety, immune and epigenetic responses, response rate, OS, PFS, and time to AML transformation.

anti-PD-1 = anti-programmed cell death 1; AML = acute myeloid leukemia; C = cycle; CDX-1401 = DEC-201/NY-ESO-1 fusion protein vaccine; DC = dendritic cell; Flt3L = FMS-related tyrosine kinase 3 ligand; GVAX = GM-CSF secreting allogenic pancreatic cancer vaccine; iNHL = indolent non-Hodgkin lymphoma; NK = natural killer; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PBMC = peripheral blood mononuclear cell; PFS = progression-free survival; PR = partial response; QoL = quality of life; SBRT = stereotactic body radiation therapy; SCCHN = squamous cell carcinoma of the head and neck; XRT = radiation therapy

2.3 BENEFIT/RISK ASSESSMENT

There are data supporting the use of the individual components of the study intervention in this cohort (ie, SBRT, CDX-301, poly-ICLC, and nivolumab), as well as clinical studies supporting the co-administration of the components as previously described (Table 2); however, the combination has not been previously studied in animal models or in human studies. Additionally, each component has been studied specifically in prostate cancer and was well tolerated (Higano et al., 2004; Brahmer et al., 2010; Patel et al., 2011; Topalian et al., 2012; Kwon et al., 2014). Toxicity profiles are non-overlapping.

Nivolumab

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy in several tumor types, including NSCLC, melanoma, RCC, and SCCHN. In confirmatory trials, nivolumab demonstrated a statistically significant improvement in overall survival (OS) as compared with the current standard of care in subjects with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or SCCHN.

For monotherapy, the safety profile is similar across tumor types. Most adverse events (AEs) were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There is no pattern in the incidence, severity, or causality AEs to nivolumab dose level. 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 (Nivolumab Investigator's Brochure, 2018).

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. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve.

Overall, these findings support a favorable benefit-risk profile for nivolumab across various tumor types. More detailed information about the known and expected benefits and risks and reasonably expected AEs of nivolumab may be found in the prescribing information (Opdivo USPI, 2018).

CDX-301

Conclusions regarding the benefit/risk of CDX-301 should be considered in the context of a drug in the early stages of development, and therefore by definition, is uncertain and evolving. CDX-301 has been well-tolerated and demonstrates the potential for utility in a number of life-threatening disease states by mobilizing and increasing the number of hematopoietic stem cells and DCs in healthy volunteers and cancer patients. Data collected to date indicate that CDX-301 has an acceptable toxicity profile, and the overall benefit/risk remains in favor of continued

clinical evaluation (CDX-301/Recombinant Human Flt3 Ligand [rhuFlt3L] Investigator's Brochure, 2018).

SBRT, CDX-301, Poly-ICLC, and Nivolumab

The safety profile of nivolumab is well characterized and manageable when administered alone or in combination, including regimens where it is administered in combination with additional immuno-oncology products. Data from studies of the individual components of the study intervention in this cohort, as well as clinical studies of the co-administration of the components of the combination, provide support for the study of this immunotherapy combination. Nonclinical data and clinical experience indicate the potential for improvement of response compared with nivolumab monotherapy. Thus, the potential benefit of this immunotherapy combination appears to outweigh the known risks of these agents and warrants clinical investigation.

3 OBJECTIVES AND ENDPOINTS

The cohort-specific objectives and endpoints are listed in Table 3.

Table 3: Cohort-Specific Objectives and Corresponding Endpoints

Objectives	Endpoints
Primary	
• To determine the safety of SBRT + CDX-301 + poly-ICLC + nivolumab in participants with mCRPC.	Refer to the core protocol.
Secondary	
• To determine the ORR of SBRT + CDX-301 + poly-ICLC + nivolumab in participants with measurable mCRPC. • To determine the DCR ≥ 9 months of SBRT + CDX-301 + poly-ICLC + nivolumab in participants with measurable mCRPC. • To evaluate the rPFS of SBRT + CDX-301 + poly-ICLC + nivolumab in participants with mCRPC. • To estimate the OS of SBRT + CDX-301 + poly-ICLC + nivolumab in participants with mCRPC.	Refer to the core protocol

Exploratory	
• To evaluate the PK of CDX-301 and/or nivolumab. • To evaluate the immunogenicity (ADA) of CDX-301 and/or nivolumab. Refer to the core protocol for overall exploratory objective(s).	• Sparse PK analysis. • Presence of ADA against CDX-301 and/or nivolumab. Refer to the core protocol for overall exploratory endpoint(s). Note that biomarker evaluation for this cohort will include DC mobilization and activation.

ADA = anti-drug antibodies; DCR = disease control rate; mCRPC = metastatic castration-resistant prostate cancer; ORR = objective response rate; OS = overall survival; PK = pharmacokinetics; rPFS = radiographic progression-free survival

4 STUDY DESIGN

4.1 OVERALL DESIGN

In this study intervention cohort, SBRT, CDX-301, and poly-ICLC will be administered during the first cycle only. Nivolumab will be administered every 4 weeks (Q4W) for up to 2 years (Figure 2), unless the participant: is no longer clinically benefiting (as evidenced by symptomatic or radiographic disease progression and/or clinical deterioration); experiences any toxicity meeting specified discontinuation criteria (see Section 6.6) or unacceptable toxicity in the best clinical discretion of the treating physician; reaches the maximum duration of study intervention; or withdraws consent. The preferred sequence when study intervention is administered on the same day (eg, Day 1) is: SBRT followed by CDX-301; followed by poly-ICLC; followed by nivolumab.

Participants will be monitored for safety and response and will be followed on-study for up to 2.5 years from the time of the initiation of study intervention. All participants will be followed for safety for at least 100 days after discontinuation of study intervention. Approximately 15 participants, including a minimum of 7 with a non-bone metastatic lesion that can be biopsied, will be enrolled in Stage 1. An additional approximately 15 participants, including a minimum of 7 with a non-bone metastatic lesion, will be enrolled in Stage 2, if the cohort is expanded.

A pre-treatment biopsy of a metastatic lesion is required for all participants, including those with bone only disease, if medically feasible. Participants must also provide consent for archival tissue from a prior biopsy or surgery for prostate cancer. An on-treatment biopsy is required, when medically feasible, usually after the second dose of study intervention. An optional biopsy may be obtained at the time of disease progression, including from participants who respond and subsequently progress following a response to treatment. The on-treatment biopsies should be taken from the same lesion as the pre-treatment biopsy when feasible.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The scientific rationale for this combination is provided in Section 2.2.5.

4.3 JUSTIFICATION FOR DOSE

The doses of CDX-301 and poly-ICLC proposed for this study have been established as being safe in previous and ongoing clinical trials (Section 4.3.2 and Section 4.3.3, respectively). Nivolumab will be administered as a fixed dose of 480 mg intravenously Q4W, an established dosing regimen and US Food and Drug Administration (FDA)-approved for a majority of approved nivolumab indications (Section 4.3.1).

SBRT has been administered in combination with CDX-301 (Ohri et al., 2018) or anti-PD-1 therapy (Luke et al, 2018; McBride et al., 2018; Theelen et al., 2018) and has been well tolerated to date without a significant safety signal. All agents are being administered at the recommended dose determined in prior studies in cancer patients and based on the safety profiles of the individual components, as well as the combinations of components that have been co-administered (Table 2), toxicities are not expected to be overlapping when administered in combination Therefore, the combination of SBRT, CDX-301, poly-ICLC, and nivolumab at the doses proposed is warranted for the evaluation of safety and efficacy in this population.

4.3.1 Rationale for Nivolumab Dose and Schedule

In the US, single-agent nivolumab was approved in 2014 at a dose of 3 mg/kg every 2 weeks (Q2W). Subsequently, population pharmacokinetics (PPK) and exposure response analyses were performed to support use of flat dosing regimens (ie, nivolumab 240 mg Q2W, 360 mg every 3 weeks [Q3W], and 480 mg Q4W) in participants with cancer. A flat dose of nivolumab 240 mg Q2W was selected since it is identical to a dose of 3 mg/kg for participants weighing 80 kg, the observed median body weight in nivolumab-treated cancer patients, while the nivolumab 360 mg Q3W and 480 mg Q4W regimens allow flexibility of dosing with less frequent visits and in combination with other agents using alternative dosing schedules to Q2W, such as ipilimumab. Using a PPK model, the overall distributions of nivolumab exposures (average steady-state concentration [Cavgss], minimum steady-state plasma concentration [Cminss], maximum steady-state plasma concentration [Cmaxss], and trough concentration after the first dose [Cmin1]) are comparable after treatment with either nivolumab 3 mg/kg or 240 mg Q2W (Nivolumab Investigator's Brochure, 2018).

Following nivolumab 480 mg Q4W, Cavgss are expected to be similar to those following nivolumab 3 mg/kg or 240 mg Q2W, while Cminss are predicted to be ~16% lower and are not considered to be clinically relevant. Cmaxss are predicted to be approximately ~43% greater relative to that following nivolumab 3 mg/kg Q2W dosing. However, the range of nivolumab exposures (median and 90% prediction intervals) following administration of 240 mg flat Q2W,

360 mg Q3W, and 480 mg Q4W regimens across the 35 to 160 kg weight range are predicted to be maintained well below the corresponding exposures observed with the well tolerated 10 mg/kg nivolumab Q2W dosing regimen (Nivolumab Investigator's Brochure, 2018).

The 240 mg Q2W dose was approved in the USPI in September 2016 for use in metastatic melanoma, NSCLC, and RCC indications. In March 2018, the 480 mg Q4W dose was approved in the USPI for use in metastatic melanoma, NSCLC, RCC, cHL, SCCHN, UC, and HCC indications (Opdivo USPI, 2018).

4.3.2 Rationale for CDX-301 Dose and Schedule

CDX-301 will be administered as a subcutaneous (SC) injection at a dose of 75 µg/kg daily (QD) for 5 days, the highest dose studied using the 5-day schedule in the phase 1 clinical study in healthy volunteers (CDX301-02), which assessed the safety, tolerability, pharmacokinetic and pharmacodynamic profile of daily SC injections of CDX-301 at multiple dose levels (1 µg/kg/day to 75 µg/kg/day) and durations (5 to 10 days; CDX-301/Recombinant Human Flt3 Ligand [rhuFlt3L] Investigator's Brochure, 2018). Notably, this is also the same dose and schedule utilized in combination with SBRT reported by Ohri et al. (Ohri et al., 2018).

Results of CDX301-02 showed that CDX-301 exhibited a typical absorption profile for SC administration with mean times to maximum serum concentration (Tmax) of 19.8 hours at 75 µg/kg/day for 5 days. Mean maximum serum concentrations (Cmax) increased linearly with dose across the dose range when administered over 5 days and was 667.4 ng/mL following 75 µg/kg/day for 5 days. Similarly, area under the curve (AUC) values increased across the entire range in a dose-independent manner. The half-life was 28 hours at 75 µg/kg/day for 5 days.

Treatment-related toxicity was infrequent and reported only at the 25 and 75 µg/kg/day dose levels (number of subjects at these dose levels was 9 and 15, respectively). One Grade 3 event, community acquired pneumonia, was considered treatment-related. However, no additional infections, dose-limiting toxicities, serious AEs (SAEs), or Grade 3 toxicities were reported. All other treatment-related AEs were Grade 1; these included lymphadenopathy in 6 subjects and single cases of diarrhea, injection site erythema, folliculitis and dry mouth. There were no reported clinically significant laboratory toxicities attributed to CDX-301.

As of October 2018, of 89 subjects (cancer patients, healthy volunteers, and stem cell donors) tested from 5 studies (Celldex-sponsored and investigator-initiated), 1 patient (receiving CDX-301 25 µg/kg/day for 10 days) has tested positive for the presence of specific anti-CDX-301 antibodies. Subsequent characterization of this patient's serum has shown the response to be non-neutralizing.

Dosing with 75 µg/kg daily for 5 days was sufficient to increase CD34+ stem cells and DCs by at least 10-fold over baseline values.

Refer to the IB (CDX-301/Recombinant Human Flt3 Ligand [rhuFlt3L] Investigator's Brochure, 2018) for an additional description of overall safety, immunogenicity, and efficacy in humans.

4.3.3 Rationale for Poly-ICLC Dose and Schedule

Poly-ICLC will be administered at a dose of 1 mg intramuscularly (IM) twice weekly for 3 weeks.

Poly-ICLC has a well-established history of use in the setting of clinical trials evaluating both its safety and efficacy in various malignancies. To date, over 85 clinical trials utilizing poly-ICLC have been registered at clinicaltrials.gov dating back to a 1996 phase 1/2 trial of poly-ICLC for use in malignant gliomas.

In its earliest use in human trials, poly-ICLC was originally employed as an inducer of IFN. Several studies were conducted, and although interest in the efficacy of poly-ICLC mediated through the mechanism of IFN-induction would subsequently diminish, it was these studies which provided the foundation for safety profiling and dosage which would be employed in later trials evaluating the efficacy of poly-ICLC via different mechanisms.

Early phase 1 trials were conducted to determine the maximum tolerated dose (MTD) under the assumption that this was also the most effective dose. It was found that the MTD was 12 mg/m^2 in cancer patients who were not terminally ill (Levine et al., 1979). Phase 1 and 2 clinical trials were subsequently conducted in patients with many types of cancers including leukemia, lymphoma, brain tumors, myeloma, juvenile laryngeal papillomatosis, renal cell carcinoma, breast cancer, ovarian cancer, and melanoma (Droller, 1987; Hawkins et al., 1985; Krown et al., 1985; Stevenson et al., 1985; Butowski et al., 2009; Salazar et al., 1996). In most of these early trials, about 6 mg/m^2 poly-ICLC was generally used intravenously. Fever, often with temperatures greater than 40°C, was a universal AE in the trials and was the primary dose-limiting factor. Other common AEs reported in these trials included nausea, vomiting, hypotension, thrombocytopenia, leukopenia, arthralgia, myalgia, and fatigue.

For patients receiving intramuscular or other non-intravenous routes of administration common side effects include discomfort at injection site, with transient discomfort and occasionally transient mild to moderate grade 1 or 2 erythematous skin reaction (Caskey et al., 2011). Alongside transient fever, patients occasionally experienced other flu-like symptoms approximately 8 to 12 hours after doses of 10 to 50 µg/kg IM, which may last for another 12 hours, but responds readily to acetaminophen or aspirin. These symptoms include mild myalgias, arthralgias, sometimes nausea, and malaise can be present during this period of time. This flu-like syndrome typically diminishes markedly after the first 2-3 poly-ICLC treatments.

Most recent and ongoing trials are using set dosing of 1-2 mg through IM, intratumoral or subcutaneous administration, well below the MTD of 12 mg/m^2 when given IV. More extensive

information regarding poly-ICLC—including pre-clinical pharmacology, toxicology and pharmacokinetics (PK), as well as multiple clinical studies—may be found in the poly-ICLC IB (Poly-ICLC Investigator's Brochure, 2018).

4.3.4 Rationale for Stereotactic Body Radiation Therapy Dose and Schedule

The optimal dose of radiation to administered in combination with immune checkpoint blockade has not been defined. As noted in the Background section, safety and intriguing activity have been demonstrated with SBRT in standard treatment doses in combination with PD-1 blockade. Therefore, this cohort will use a similar approach to that previously described (Luke et al., 2018) and employ standard treatment doses of SBRT. SBRT offers ablative dose-escalation to tumor targets with simultaneous dose-restraint to normal tissues, which is not possible using conventional radiotherapy. SBRT utilizes high-precision radiotherapy delivery machines, integrated image guidance systems, advanced planning software, and a high level of professional and technical expertise. Unlike conventional radiation therapy, which is delivered in multiple fractions of 1.8-2 Gy, SBRT is delivered in 1 to 5 fractions of typically 8 Gy or greater. Participants will undergo SBRT to up to 4 sites of metastases, as long as at least 1 metastasis remains outside the irradiated target. SBRT will be delivered in 3 to 5 fractions. SBRT 5 fraction regimens should deliver a total dose of 30 to 50 Gy. SBRT 3 fraction regimens should deliver a total dose of 24-45 Gy. Dose selection will depend on adequate sparing of normal tissue with maximization of dose delivered to metastatic sites. A biologically equivalent dose (BED) to tumor of > 100 Gy (for an alpha–beta ratio of 3) is a goal but is not required. Dose constraints per NRG (RTOG) B001 are recommended. Suggested regimens based on site of metastasis are defined as follows:

- 45 Gy in 3 fractions for peripheral lung, liver, and abdominal/pelvic;
- 50 Gy in 5 fractions for central lung and mediastinal/cervical;
- 30 Gy in 3 fractions for osseous and spinal/paraspinal

The optimal sequence of radiation and immune checkpoint blockade has not been established. Modeling studies suggest that immune checkpoint (Kosinsky et al., 2018) blockade prior to, or concurrent with, radiation maximizes the potential synergistic effects of these modalities. Given these considerations, as well as emerging data in model systems and patients also supporting a concurrent rather than sequential approach (Azad et al., 2017; Aliru et al., 2018; Pinnamaneni et al., 2017), this cohort will employ concurrent treatment.

4.4 TREATMENT BEYOND DISEASE PROGRESSION

Refer to the core protocol.

4.5 END OF STUDY DEFINITION

Refer to the core protocol for the end of study definition.

The total length of this study cohort, from screening of the first participant to the end of the cohort, is expected to be approximately 3 years, 9 months.

5 STUDY POPULATION

Prospective requests for approval of protocol deviations to recruitment and enrollment criteria, also known as waivers or exemptions, is not allowed.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all the following criteria apply:

5.1.1 Common Inclusion Criteria

1. Participant must be ≥ 18 years of age at the time the informed consent is signed.
2. Participants must agree to use an adequate method of contraception as outlined in Appendix 6 of the core protocol starting with the first dose of study intervention and for at least 7 months after the last dose of study intervention and refrain from donating sperm during this period.
   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the participant.
3. Participants must be able and willing to comply with the study visit schedule and study procedures.
4. Histologically documented adenocarcinoma of the prostate.
5. Metastatic castration resistant prostate cancer with castrate-level testosterone (< 50 ng/dL) at screening.
6. Have received and progressed on prior secondary androgen receptor signaling inhibitor therapy (eg, abiraterone, enzalutamide, apalutamide). Progression is defined by one or more of the following 3 criteria:
   a. Prostate-specific antigen (PSA) ≥ 1.0 ng/mL and rising PSA by at least 2 consecutive measurements a minimum of 1-week apart.
   b. Soft tissue progression as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer et al., 2009).
   c. Bone disease progression as defined by 2 new bone lesions (as per Prostate Cancer Clinical Trials Working Group 3 [PCWG3; Scher et al., 2016]).
7. Have measurable disease or non-measurable disease based on PCWG3-modified RECIST 1.1.
8. Provide fresh pre-treatment core needle or incisional biopsy of a metastatic tumor lesion not previously irradiated. Fine needle aspiration is not acceptable.

a. Additionally, if a pre-treatment biopsy is not medically feasible for participants with bone only disease, formalin-fixed paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 10 slides containing unstained, freshly cut, serial sections must be provided.

b. For all participants, in addition to fresh pre-treatment biopsy, consent for archival tissue is required.

9. Must be willing to undergo tumor biopsy(ies) on treatment, if medically feasible.
10. Participants must discontinue antiandrogen therapy (ie, bicalutamide, flutamide, nilutamide) at least 4-6 weeks prior to registration with no evidence of PSA decline after washout.
    a. Bicalutamide: Washout period at least 6 weeks
    b. Flutamide and nilutamide: Washout period at least 4 weeks
11. Participants must discontinue therapies for mCRPC for 5 half-lives or 28 days, whichever is shorter.
    a. Participants will remain on gonadotropin-releasing hormone (GnRH) agents throughout this study.
    b. Prior chemotherapy is allowed if no progression of disease on chemotherapy as defined by PCWG3-modified RECIST 1.1.
    c. Prior treatment with sipuleucel-T, radium-223, or poly adenosine diphosphate (ADP)-ribose polymerase (PARP) inhibitor (eg, olaparib) is allowed.
    d. Tissue biopsy may be performed during washout period.
12. Participants with prior or concurrent malignancies are permitted if any one of the following applies:
    a. Previously treated malignancy for which all treatment of that malignancy was completed at least 2 years before enrollment and no evidence of disease exists, or
    b. With agreement from the Medical Monitor and Principal Investigator (PI), participants who have a concurrent malignancy that is clinically stable and does not require tumor-directed treatment are eligible to participate if the risk of the prior malignancy interfering with either safety or efficacy endpoints is very low, or
    c. With agreement from the Medical Monitor and PI, other malignancies may be permitted if the risk of the prior malignancy interfering with either safety or efficacy end points is very low.
13. Have a performance status of 0 or 1 according to the Eastern Cooperative Oncology Group (ECOG) scale.
14. Demonstrate adequate organ function on screening laboratory tests performed within 14 days of treatment initiation and as evidenced by:
    a. Hemoglobin $\geq$ 9.0 g/dL or $\geq$ 5.6 mmol/L without transfusion or erythropoietin (EPO) dependency (within $\leq$ 7 days of assessment)

b. Absolute neutrophil count ≥ 1,500/mm^3 without growth factor support (within < 28 days of assessment)

c. Platelet count ≥ 100,000/mm^3

d. Estimated glomerular filtration rate (GFR) ≥ 45 mL/min using the Cockcroft-Gault formula

e. Serum total bilirubin < 1.5 x upper limit of normal (ULN) or ≤ 2.0 x ULN for participants with liver metastases

   i. Participants with Gilbert's syndrome must have ≤ 3 x ULN and no liver lesions

f. Aspartate aminotransferase (AST) (SGOT) and alanine aminotransferase (ALT) (SGPT) ≤ 3.0 x ULN or ≤ 5.0 x ULN for participants with liver metastases.

g. Albumin ≥ 2.5 mg/dL.

h. International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 x ULN unless participant is receiving anticoagulant therapy, as long as PT is within therapeutic range of intended use of anticoagulants.

i. Activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN unless participant is receiving anticoagulant therapy, as long as PTT is within therapeutic range of intended use of anticoagulants.

15. Willing and capable of giving signed informed consent as described in Appendix 1 of the core protocol, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.1.2 Combination-specific Inclusion Criteria

1. Participants must have at least one lesion amenable to SBRT as determined by the treating radiation oncologist. Participants must have lesions in organs/locations that can be treated with at least 30 Gy.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

5.2.1 Common Exclusion Criteria

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.

   a. Recent or concurrent non-therapeutic investigational agents that are not anticipated to interfere with study intervention, such as certain investigational imaging tracers, may be permitted with written agreement from the Medical Monitor.

2. Has a diagnosis of immunodeficiency or conditions that need systemic corticosteroid replacement therapy > 10 mg/day prednisone (or equivalent) or other immunosuppressive medications within 28 days prior to the first dose of study intervention. Inhaled steroids are permitted if necessary.
3. Has any active known or suspected autoimmune disease. Participants with vitiligo, type I diabetes mellitus, controlled autoimmune hypothyroidism, psoriasis not requiring systemic treatment, or other conditions under control are permitted to enroll. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy ≤ 10 mg of prednisone/day for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
4. Has a known history of active TB (*Bacillus Tuberculosis*).
5. Has known history of, or any evidence of active, non-infectious pneumonitis.
6. Has an active infection requiring systemic therapy.
7. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the participant's participation for the full duration of the trial, or is not in the best interest of the participant to participate, in the opinion of the treating Investigator.
8. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
9. Is expecting to father children within the projected duration of the trial, starting with the pre-screening or screening visit through 7 months after the last dose of study intervention.
10. Known history of testing positive for human immunodeficiency virus (HIV), known acquired immunodeficiency syndrome (AIDS), or any positive test for hepatitis B or hepatitis C virus representing acute or chronic disease.
11. Has received a live vaccine within 30 days of planned start of study intervention.

    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (eg, Flu-Mist®) are live attenuated vaccines, and are not allowed.
12. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of study intervention and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to study intervention. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
13. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (ie, ≤ Grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier.
    a. Participants with controlled autoimmune disease as described in exclusion criterion #3 are permitted to enroll.

14. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (ie, ≤ Grade 1 or at baseline) from AEs due to a previously administered agent.
    a. Note: Participants with ≤ Grade 2 neuropathy and/or hearing loss are an exception to this criterion and may qualify for the study.
    b. Note: If a participant received major surgery, he must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
15. History of allergy to any of the study intervention components.

5.2.2 Combination-specific Exclusion Criteria

1. Has had prior therapy with any anti-PD-1 or anti-PD-L1 antibody (prior therapy with an anti-CTLA-4 antibody is permitted).
2. Has a history of acute myeloid leukemia (AML).

5.3 LIFESTYLE CONSIDERATIONS

No restrictions are required.

5.4 SCREEN FAILURES

Refer to the core protocol.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

The study interventions to be administered in this study are summarized in Table 4.

Table 4: Study Intervention

Study Intervention Name	Dosage Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Sourcing
SBRT	30-50 Gy in 1-5 doses. Radiation will start on Day 1 or 2				
CDX-301	Sterile solution for single use. Single-use vial containing CDX-301 in buffered solution composed of sodium phosphate and sodium chloride, with a pH of 7.0	2.5 mg/mL	75 µg/kg	SC	Celldex Therapeutics

Study Intervention Name	Dosage Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Sourcing
Poly-ICLC	Single-dose vial containing opalescent white suspension poly-IC, poly-L-lysine, and sodium carboxymethylcelluose in 0.9% sodium chloride, adjusted to a pH of 6 – 8 with sodium hydroxide	2 mg/mL	1 mg	IM	Oncovir, Inc.
Nivolumab	Aqueous solution	10 mg/mL	480 mg	IV infusion	Bristol-Myers Squibb

Gy = gray; IV = intravenous(ly); IM = intramuscular(ly); SBRT = stereotactic body radiation therapy; SC = subcutaneous(ly)

SBRT, CDX-301, and poly-ICLC will be administered during the first cycle only. The preferred sequence when study intervention is administered on the same day (eg, Day 1) is: SBRT followed by CDX-301; followed by poly-ICLC; followed by nivolumab:

- Radiation therapy will be administered at 30 – 50 Gy in 1 – 5 doses, starting on Day 1 or 2 of Cycle 1.
- CDX-301 will be administered at a dose of 75 µg/kg SC QD x 5 days (Days 1 – 5 [ie, Monday – Friday] of Cycle 1).
- Poly-ICLC will be administered at a dose of 1 mg intramuscularly (IM) twice weekly for 3 weeks (ie, Days 1, 5, 8, 12, 15, and 19) starting on Day 1 of Cycle 1.
- Nivolumab will be administered at a dose of 480 mg IV over approximately 30 minutes Q4W, starting on Day 1 of Cycle 1, for up to 2 years, unless the participant: is no longer clinically benefiting (as evidenced by symptomatic or radiographic disease progression and/or clinical deterioration); experiences any toxicity meeting specified discontinuation criteria (see Section 6.6) or unacceptable toxicity in the best clinical discretion of the treating physician; reaches the maximum duration of study intervention; or withdraws consent. A cycle is defined as 4 calendar weeks.

Administration of study intervention will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Refer to the core protocol for general guidance on handling, storage, and accountability.

CDX-301 should be stored in a secure, locked area at 2-8°C and protected from light. CDX-301 should not be frozen, and CDX-301 vials should not be shaken. CDX-301 liquid should be withdrawn from vial gently, avoiding foaming and excess shearing.

Poly-ICLC should be stored refrigerated at 2-8°C but should not be frozen.

Nivolumab must be stored at 2°-8°C and protected from light and freezing.

The instructions for reconstitution and administration of the study intervention are described in the Pharmacy Manual(s).

6.3 RANDOMIZATION AND BLINDING

This is not a randomized study, and study intervention will be administered in an open-label fashion.

6.4 STUDY INTERVENTION COMPLIANCE

Study intervention will be administered by authorized site personnel and tracked using drug accountability records. No additional measures of compliance will be instituted.

6.5 CONCOMITANT THERAPY

Refer to the core protocol.

6.5.1 Permitted Therapy

Refer to the core protocol.

6.5.2 Prohibited Therapy

Refer to the core protocol.

6.6 DOSE MODIFICATIONS

6.6.1 Dose Modifications for the Combination of Nivolumab, CDX-301, and Poly-ICLC

There will be no dose escalation or dose reductions in this study.

The initial 6 participants enrolled in this cohort will be observed for the occurrence of any of the AEs described in Table 5 that are observed from the beginning of treatment through completion of the first cycle of nivolumab (ie, 4 weeks) and that are considered by the Investigator to be possibly, probably, or definitely related to nivolumab, CDX-301, poly-ICLC, or the immunotherapy combination, unless there is a clear alternative explanation.

After enrollment of the initial 6 participants, enrollment will pause until all 6 participants have completed Cycle 1 (ie, 4 weeks). During the pause, new participants may be consented and screened, but not initiated on study intervention. If 1 or no AEs described in Table 5 are observed in the first 6 participants, enrollment will continue as planned until a total of

approximately 15 participants are enrolled. If AEs described in Table 5 are observed in 2 or more of the first 6 participants, enrollment into the cohort will be suspended, and the Safety Assessment Committee (refer to Section 9.5.1 of the core protocol) will be convened to review the available data and provide a recommendation, which may include, but is not limited to, modification or discontinuation of the cohort.

Participants who experience any AE described in Table 5 will be discontinued from all study intervention and should continue follow-up assessments as outlined in the SOA (Section 1.3).

Grade 3 and 4 toxicities are observed in all trials of nivolumab in multiple tumor types. As such toxicities are anticipated; however, given the unique nature of this protocol, monitoring for AEs described in Table 5 will continue throughout the study.

The Investigator may attribute each AE to the combination or any individual component of the study intervention. Study participants may not have any dose escalations or reductions of nivolumab, CDX-301, or poly-ICLC in this study. If an Investigator believes a toxicity is uniquely related to one agent, then appropriate documentation is required regarding the drug to which the Investigator is attributing the AE. The following retreatment requirements will apply:

- During Cycle 1 if, in the opinion of the Investigator, the toxicity is related to CDX-301 and/or poly-ICLC, then CDX-301 and/or poly-ICLC drugs should be withheld (eg, skipped) according to recommended dose modifications.
- Cycle 2, in which only nivolumab is administered, may commence as scheduled provided the participant meets the retreatment criteria for nivolumab.
    - Starting with Cycle 2 if toxicity does not resolve or the criteria for resuming study intervention are not met within 8 weeks after the last dose of nivolumab, the participant must be discontinued from nivolumab therapy, unless written approval to restart therapy is provided by the Medical Monitor.

The anticipated important safety risks associated with the administration of SBRT, nivolumab, CDX-301, and/or poly-ICLC, as well as the measures to be taken, are outlined in the following sections. Guidance with respect to the individual agents is provided in Section 6.6.3, Section 6.6.4, and Section 6.6.5, respectively. Refer to the USPI for nivolumab (Opdivo USPI, 2018) to the Investigator's Brochures for nivolumab, CDX-301, and poly-ICLC for complete summaries of safety information.

Table 5: Toxicity Criteria Requiring Permanent Treatment Discontinuation

Participants should be monitored for the occurrence of any of the following AEs that are considered by the Investigator to be possibly, probably, or definitely related to nivolumab, CDX-301, poly-ICLC, or the immunotherapy combination. Treatment with all study intervention should be permanently discontinued for the following:

• Grade 4 non-hematological toxicity (not laboratory)
• Grade 4 hematologic toxicity lasting ≥ 7 days
• Grade 3 thrombocytopenia in the presence of clinically significant active bleeding (eg, requiring transfusion or hospitalization)
• Any non-hematologic toxicity ≥ Grade 3 in severity, with the following exceptions:
  ○ Grade 3 fatigue lasting ≤ 3 days
  ○ Grade 3 nausea, vomiting, or diarrhea lasting ≤ 3 days
  ○ Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care
  ○ Grade 4 fever
  ○ Grade 4 flu-like symptoms lasting ≥ 48 hours
• Any new Grade 3 or Grade 4 non-hematologic laboratory abnormality, if
  ○ the abnormality leads to hospitalization, or
  ○ the abnormality persists for > 1 week and is believed to be clinically significant. For example, exceptions would include asymptomatic pancreatitis.
• Febrile neutropenia Grade 3 or Grade 4
• Any elevated AST or ALT laboratory value that is ≥ 3 × ULN and an elevated total bilirubin lab value that is ≥ 2 × ULN and an alkaline phosphatase lab value that is < 2 × ULN, in which no alternative reasons can be found to explain the combination of increased AST/ALT and total bilirubin, such as viral hepatitis A, B or C, preexisting or acute liver diseases, pre-existing known liver metastases, or another drug capable of causing the observed injury
• Grade 5 toxicity

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

6.6.1.1 Potential for Overlapping Toxicities with the Combination of SBRT, Nivolumab, CDX-301, and Poly-ICLC

In general, the toxicities associated with the monotherapy administration of nivolumab, CDX-301, and poly-ICLC are not expected to be overlapping when administered in combination.

The safety data for nivolumab are described in the USPI (Opdivo USPI, 2018). Nivolumab therapy is associated with immune-mediated adverse reactions, which can be severe and fatal in some cases. With appropriate medical therapy, immune-related adverse reactions resolved in most cases. Immune-mediated adverse reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, endocrinopathies, hepatitis, dermatitis (including toxic epidermal necrolysis [TEN] and Stevens-Johnson syndrome [SJS]), and neuropathy. The safety profile of nivolumab combination therapy varies with the agent combined with nivolumab but is generally consistent with the safety profiles observed with either agent alone and, in some cases, both frequency and severity of AEs were greater than that observed with either agent alone.

In human studies to date, Flt3L has been well tolerated, with many AEs attributable to patients' underlying malignancy or other compounds/therapies being administered concomitantly, and no dose reductions of Flt3L for toxicity were reported in any of these trials. Erythematous nodules of up to 1 to 2 cm at the skin injection sites lasting several days were the only manifestation of toxicity in most patients. One patient who injected doses into the same area daily for 3 consecutive days developed diffuse erythema of the upper arm and adenopathy in the axilla that resolved spontaneously. Arthralgias, myalgias, and fever were not reported, nor were liver function test abnormalities. With CDX-301 administration, specifically, leukocytosis, especially monocytosis, is expected during administration. Injection site reactions have been reported and are generally mild to moderate, but occasionally severe. Lymphadenopathy occurred in < 20% of study participants, was not associated with AEs, and resolved after discontinuation of treatment (CDX-301/Recombinant Human Flt3 Ligand [rhuFlt3L] Investigator's Brochure, 2018).

In most of the early trials of poly-ICLC, about 6 mg/m^2 poly-ICLC was generally administered IV. Fever, often with temperatures greater than 40°C, was a universal AE in these trials and was the primary dose-limiting factor. Other common AEs reported in these trials included nausea, vomiting, hypotension, thrombocytopenia, leukopenia, arthralgia, myalgia, and fatigue (Poly-ICLC Investigator's Brochure, 2018).

SBRT has been associated with mild to moderate GU and GI acute and late toxicities in patients with localized prostate cancer (Syed et al., 2017; Haque et al., 2017; King et al., 2013). The incidence of ≥ Grade 3 acute toxicities was typically < 5%, while at least 1 late urinary ≥ Grade 3 late toxicity has been reported in the majority of studies (Syed et al., 2017).

6.6.1.2 Dose Modifications and Toxicity Management for Adverse Events Associated with the Combination of Nivolumab, CDX-301, and Poly-ICLC

Immuno-oncology agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms (Appendix B-1) have been developed to assist Investigators in assessing and managing the following groups of drug-related AEs:

- Immune-mediated colitis
- Immune-mediated nephritis and renal dysfunction
- Immune-mediated pneumonitis
- Immune-mediated hepatitis

- Immune-mediated endocrinopathies (hypophysitis, adrenal insufficiency, hypothyroidism and hyperthyroidism, Type 1 diabetes mellitus)
- Immune-mediated skin adverse reactions
- Immune-mediated encephalitis

6.6.1.3 Dose Modifications and Toxicity Management for Infusion/Injection-related Reactions Associated with the Administration of CDX-301, Poly-ICLC, and/or Nivolumab

Interrupt or slow the rate of infusion in participants with mild or moderate infusion reactions. Discontinue the immunotherapy combination in participants with severe or life-threatening infusion reactions.

All Grade 3 or 4 infusion reactions must be reported within 24 hours to the study Medical Monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded as described in Section 10.5.3 of the core protocol.

Dose modification and toxicity management guidelines for infusion/injection-related reactions are provided in Table 6.

Table 6: Dose Modification and Toxicity Management Guidelines for Infusion/Injection-related Reactions Associated with the Administration of CDX-301, Poly-ICLC, and/or Nivolumab

Grade (NCI CTCAE v 5.0)	**Treatment**	**Premedication at Subsequent Dosing**
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	**Stop Infusion** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study intervention**	Participant may be premedicated according to local treatment guidelines
Grades 3 or 4 <u>Grade 3</u>: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) <u>Grade 4</u>: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion** Administer urgent medical therapy as appropriate/clinically indicated Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator Hospitalization may be indicated **In cases of anaphylaxis, epinephrine should be used immediately **Participant is permanently discontinued from further study intervention**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; NSAIDs = nonsteroidal anti-inflammatory drugs; IV = intravenous

6.6.1.4 Dose Delays and Interruptions of Nivolumab, CDX-301, and Poly-ICLC

Dose delays and interruptions are permitted for toxicity reasons (see Section 6.6.3 and Section 6.6.4).

The Investigator may attribute each AE to the combination or to either individual intervention.

- If, in the opinion of the Investigator, the toxicity is related to the combination of the agents, then all drugs should be held according to recommended dose modifications.
- If the toxicity is considered clearly related to 1 agent, but not the others, then the other agents can continue unless toxicity related to that study intervention would warrant a dose delay.

6.6.2 Dose Modification for SBRT

The short duration time of this treatment may not require adjustments and may limit the need for dose modification, but due to organ sites involved with the treatment, it may be necessary to modify the dosage to address acute AEs related to SBRT. Dose modification of SBRT will be managed according to institutional guidelines.

Appropriate documentation is required regarding the component of treatment to which the Investigator is attributing the AE. If toxicity does not resolve or the criteria for resuming study intervention are not met within 8 weeks after the last dose, the participant must be discontinued from the combination therapy.

Dose delays and interruptions for reasons other than toxicity, such as surgical procedures, may be allowed with Medical Monitor approval. The acceptable length of interruption will depend on agreement between Investigator and Medical Monitor.

6.6.3 Dose Modifications for Nivolumab

This study will include set dosing for nivolumab (480 mg Q4W). Dose escalation or reduction of nivolumab will not be allowed. If toxicity does not resolve or the criteria for resuming study intervention are not met within 8 weeks from the last dose, the participant must discontinue nivolumab therapy, unless written approval to restart therapy is provided by the Medical Monitor.

Specific anticipated or potential toxicities associated with the administration of nivolumab, as well as the measures to be taken to avoid or minimize such toxicity in this trial, are described in Table 7.

AEs associated with nivolumab exposure may represent an immunologic etiology. These immune-related adverse events (irAEs) may occur shortly after the first dose or several months

after the last dose of treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, drug-related AEs have included pulmonary toxicity, renal toxicity (including acute renal failure), endocrine abnormalities, gastrointestinal toxicity, dermatologic toxicity (including rash), and hepatotoxicity. For nivolumab monotherapy, as well as when administered in combination, the majority of these AEs have been managed successfully with supportive care and, in more severe cases, a combination of dose delay, permanent discontinuation, and/or use of corticosteroids or hormone replacement therapy (endocrinopathies). For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, and skin biopsy may be included as part of the evaluation.

Dose modification and toxicity management guidelines for irAEs associated with nivolumab are provided in Table 7.

Table 7: Dose Modification and Toxicity Management Guidelines for Adverse Events Associated with Nivolumab

Adverse Reaction	Severity[a]	Dose Modifications
Colitis	Grade 2 diarrhea or colitis	Withhold dose[b]
	Grade 3 diarrhea or colitis	Withhold dose[b]
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose[b]
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hepatitis/non-HCC	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal (ULN) or total bilirubin more than 1.5 and up to 3 times the ULN	Withhold dose[b]
	AST or ALT more than 5 times the ULN or total bilirubin more than 3 times the ULN	Permanently discontinue
Hepatitis/HCC	• If AST/ALT is within normal limits at baseline and increases to more than 3 and up to 5 times the ULN • If AST/ALT is more than 1 and up to 3 times ULN at baseline and increases to more than 5 and up to 10 times the ULN • If AST/ALT is more than 3 and up to 5 times ULN at baseline and increases to more than 8 and up to 10 times the ULN	Withhold dose[c]
	If AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose[b]
	Grade 4 hypophysitis	Permanently discontinue

Adverse Reaction	Severity[a]	Dose Modifications
Adrenal insufficiency	Grade 2 adrenal insufficiency	Withhold dose[b]
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Type 1 diabetes mellitus	Grade 3 hyperglycemia	Withhold dose[b]
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and renal dysfunction	Serum creatinine more than 1.5 and up to 6 times the ULN	Withhold dose[b]
	Serum creatinine more than 6 times the ULN	Permanently discontinue
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose[b]
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue
Encephalitis	New onset moderate or severe neurologic signs or symptoms	Withhold dose[b]
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction • First occurrence • Recurrence of the same Grade 3 adverse reaction	Withhold dose[b] Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Grade 3 myocarditis	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

Source: Opdivo USPI, 2018

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HCC = hepatocellular carcinoma; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; ULN = upper limit of normal

[a] Guidelines based on toxicity graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), where applicable.

[b] Resume treatment when adverse reaction improves to Grade 0 or 1.

[c] Resume treatment when AST/ALT return(s) to baseline.

6.6.4 Dose Modifications for CDX-301

Dose escalation or reduction of CDX-301 will not be allowed in this study. Doses of CDX-301 should be withheld (eg, skipped) for toxicity attributed to CDX-301 (Table 8), and doses that are skipped should not be made up. Toxicities attributed to CDX-301 that require dose delays greater than 6 weeks will require Medical Monitor approval for the participant to restart treatment.

Leukocytosis, especially monocytosis, is expected during administration of CDX-301 and may be particularly pronounced when combined with other hematopoietic growth factors.

Hematological parameters, including white blood cell (WBC) and differential, should be monitored in participants receiving CDX-301.

Specific anticipated or potential toxicities associated with the administration of CDX-301, as well as the measures to be taken to avoid or minimize such toxicity in this trial, are described in Table 8.

Table 8: Dose Modification and Toxicity Management Guidelines for Adverse Events Associated with CDX-301

Adverse Reaction	Severity	Dose Modifications
Leukocytosis	WBC count > 50,000 cells/mm^3	Withhold (skip) dose[a]
Injection site reaction	Grade 1 or 2	No action required regarding CDX-301 dose. Pre-medication with diphenhydramine may be considered for participants who experience local reactions after treatment with CDX-301
	Grade 3	Permanently discontinue
	Grade 4	Permanently discontinue
Other ≥ Grade 2 adverse reaction	• First occurrence	Withhold (skip) dose[a]
	• Recurrence of the same ≥ Grade 2 adverse reaction	Permanently discontinue

WBC = white blood cell

[a] Resume treatment at the same CDX-301 dose level when adverse reaction returns to baseline, except for instances where the potential recurrence of the event poses an undue risk for the participant. Doses that are withheld (eg, skipped) should not be made up.

6.6.5 Dose Modifications for Poly-ICLC

Dose escalation or reduction of poly-ICLC will not be allowed in this study. Poly-ICLC may be withheld (eg, skipped) if the participant experiences ≥ Grade 2 AEs considered at least possibly related to poly-ICLC. Doses of poly-ICLC that are skipped should not be made up. Toxicities attributed to poly-ICLC that require dose delays greater than 6 weeks will require Medical Monitor approval for the participant to restart treatment.

7 DISCONTINUATIONS OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Refer to the core protocol.

In addition to the discontinuation criteria described in the core protocol, refer to Table 5, Section 6.6.3, Section 6.6.4, and Section 6.6.5 for management of toxicities requiring permanent discontinuation of nivolumab, CDX-301, and/or poly-ICLC.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM STUDY

Refer to the core protocol.

7.3 LOST TO FOLLOW-UP

Refer to the core protocol.

8 STUDY ASSESSMENTS AND PROCEDURES

Refer to the core protocol. Any combination-specific supplementary information or modifications from the core protocol are described in the following sections.

In this study cohort, the time between nivolumab doses must not be less than 24 days.

8.1 EFFICACY ASSESSMENTS

Refer to the core protocol.

8.1.1 Laboratory Assessments of Clinical Activity

Samples for the laboratory assessments of clinical activity and hormone levels in Table 9 will be sent to the study site's local laboratory for analysis:

Table 9: Laboratory Tests Sent to the Study Site's Local Laboratory for Analysis of Disease-related Endpoints

Profile	Laboratory Test
Clinical activity	PSA
Hormone levels	testosterone

PSA = prostate-specific antigen

8.2 SAFETY ASSESSMENTS

Refer to the core protocol.

8.2.1 Clinical Safety Laboratory Assessments

8.2.1.1 Local Laboratory Assessments

Samples for the laboratory tests in Table 10 will be sent to the study site's local laboratory for analysis:

Table 10: Laboratory Tests Sent to the Study Site's Local Laboratory for Analysis of Safety

Profile	Laboratory Test
Hematology	RBC count hemoglobin hematocrit WBC count with automated differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells) platelet count manual differential, if clinically indicated
Clinical Chemistry (Serum or Plasma)	sodium potassium chloride bicarbonate glucose BUN or urea creatinine total protein albumin calcium total bilirubin alkaline phosphatase ALT AST LDH TSH (T3 and FT4 should be checked if TSH is outside the normal range) coagulation assessments (PT, PTT, INR)[a]
Urinalysis	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; TSH = thyroid stimulating hormone; WBC = white blood cell

[a] Coagulation assessment not required during treatment phase unless indicated

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Refer to the core protocol for the SAE and AE collection periods and for details regarding safety reporting.

8.3.4 Regulatory Reporting Requirements for SAEs

Refer to the core protocol for the regulatory reporting requirements for SAEs.

For this cohort, the Parker Institute for Cancer Immunotherapy Pharmacovigilance Group will report SAEs to regulatory authorities, the overall PI, Bristol-Myers Squibb, Celldex Therapeutics, Oncovir, Inc., and the Institutional Review Board/Independent Ethics Committee (IRB/IEC), as appropriate. The process for such reporting, including contact information and

specific instructions for reporting to each of these organizations, is described in the Safety Monitoring Plan.

8.3.7 Adverse Events of Special Interest

There are no identified adverse events of special interest for this immunotherapy combination.

8.4 TREATMENT OF OVERDOSE

Refer to the core protocol.

8.5 PHARMACOKINETICS

Sparse PK blood sampling will be collected according to the SOA to assess the PK of CDX-301 and/or nivolumab.

PK profiles for CDX-301 and/or nivolumab may be performed using a validated assay method under the supervision of the Sponsor's designee.

8.6 ANTI-DRUG ANTIBODIES

Immunogenicity samples will be collected according to the SOA to enable evaluation of anti-drug antibodies (ADA) to either CDX-301 and/or nivolumab. Additionally, blood samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples may be tested by the Sponsor's designee.

The detection and characterization of antibodies to CDX-301 and/or nivolumab may be performed using a validated assay method under the supervision of the Sponsor's designee.

8.7 BIOMARKERS

Refer to the core protocol.

Immune profiling may be performed, including evaluation of dendritic cell numbers and activation using flow cytometry or other assays.

8.8 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Refer to the core protocol.

9 STATISTICAL CONSIDERATIONS

Refer to the core protocol.

9.5.1 Interim Safety Monitoring

Refer to the core protocol for details related to the Safety Assessment Committee (SAC), the committee charged with safety review for this study.

With the inclusion of a safety period for the first 6 participant for this study cohort (see Section 6.6.1), the likelihood of proceeding to full enrollment decreases as the risk of toxicity from an AE described in Table 5 increases, as demonstrated in Table 11.

Table 11: Probability of Proceeding to Full Enrollment

True Risk of Toxicity	0.10	0.20	0.30	0.40	0.50	0.60
Probability of Full Enrollment	0.89	0.66	0.42	0.23	0.11	0.04

Assumes P(X≤1) where X is a binomial random variable with sample size n = 6 and p = true risk of toxicity.

Table 12 shows the width of 95% confidence intervals calculated for possible observed rates of AEs described in Table 5 within the study.

Table 12: Incidence with 95% Confidence Intervals of Possible Observed Adverse Events Described in Table 5

Number of Participants with Adverse Events[a]/Number of Participants	**Incidence of Adverse Events[a]**	**95% Confidence Interval[b]**
0/6	0	[0, 0.39]
1/6	0.17	[0.03, 0.56]
2/6	0.33	[0.10, 0.70]
3/6	0.50	[0.19, 0.81]

[a] Adverse events described in Table 5

[b] Wilson method for computing confidence interval

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Refer to the core protocol for the following appendices:

Appendix 1: Regulatory, Ethical and Study Oversight Considerations

Appendix 2: Eastern Cooperative Oncology Group (ECOG) Performance Status

Appendix 3: RECIST Criteria (Version 1.1) with Modifications as Recommended by PCWG3

Appendix 4: Clinical Laboratory Tests

Appendix 5: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Appendix 6: Contraceptive Guidance and Collection of Pregnancy Information

Appendix 7: Genetics

10.1 APPENDIX B-1: MANAGEMENT ALGORITHMS

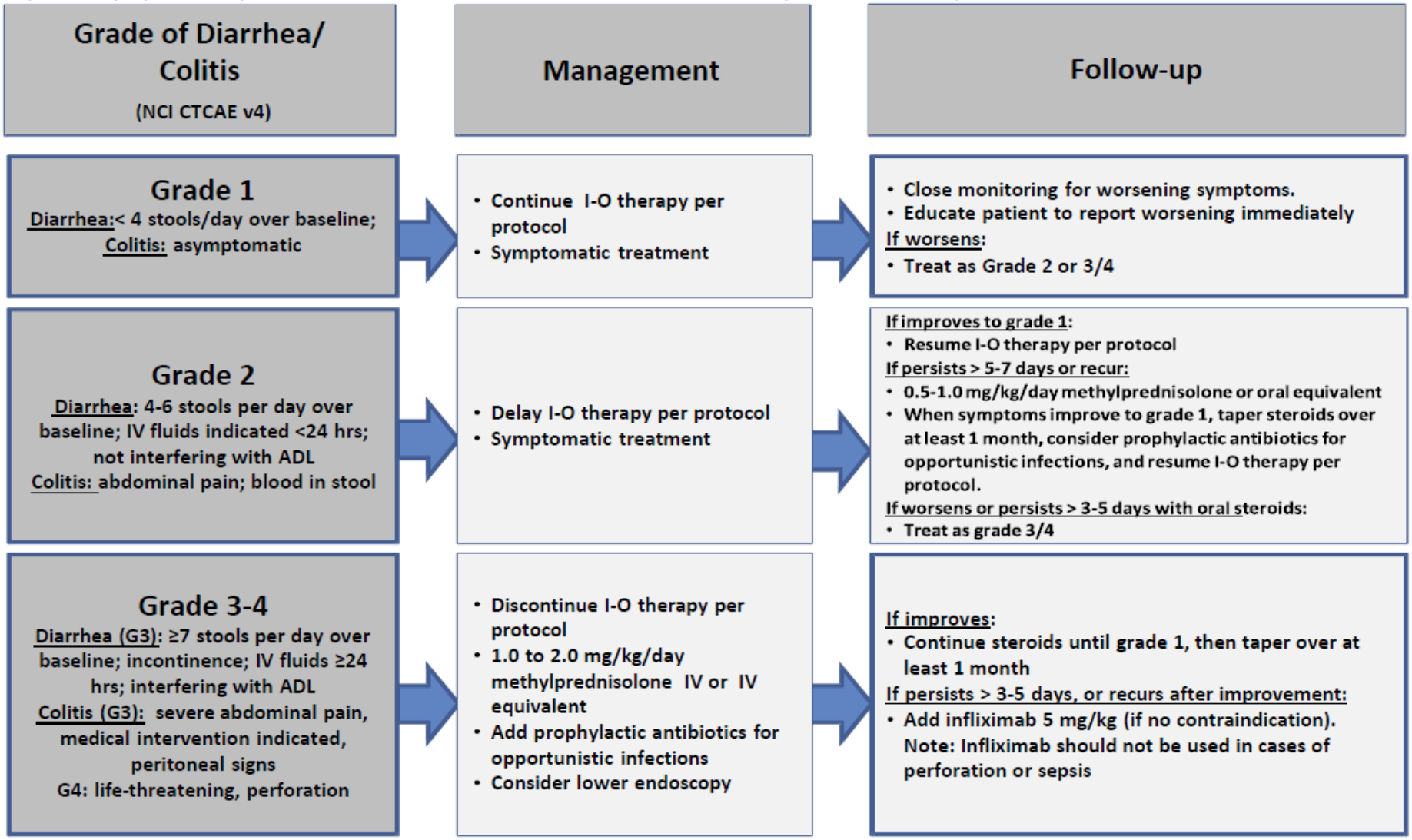
Management algorithms have been developed to provide guidance for Investigators in assessing and managing immune-mediated events in participants receiving nivolumab. Section 6.6.3 describes the criteria for dose delay and discontinuation to be followed for nivolumab in this cohort. These algorithms are intended to provide clinical recommendations. In cases in which the modification criteria in Section 6.6.3 and the algorithms differ, the criteria in Section 6.6.3 should take precedence.

The management algorithms are provided for the following groups of drug-related AEs:

- Immune-mediated gastrointestinal adverse events (diarrhea, colitis)
- Immune-mediated renal adverse events (nephritis and renal dysfunction)
- Immune-mediated pulmonary adverse events (pneumonitis)
- Immune-mediated hepatic adverse events (hepatitis)
- Immune-mediated endocrinopathy adverse events (hypophysitis, adrenal insufficiency, hypothyroidism and hyperthyroidism, Type 1 diabetes mellitus)
- Immune-mediated skin adverse events
- Immune-mediated neurologic adverse events (encephalitis)

GI Adverse Event Management Algorithm

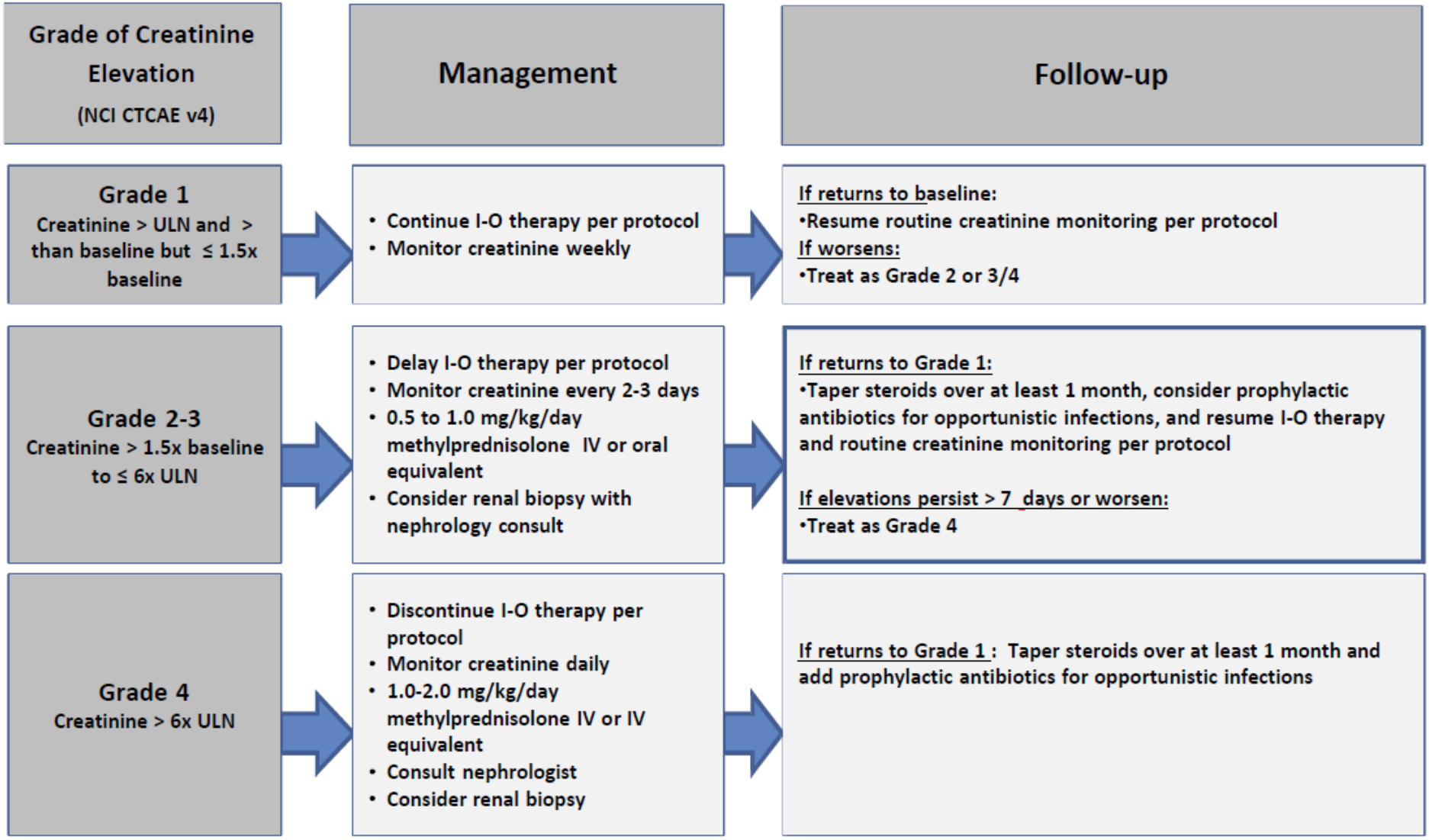
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

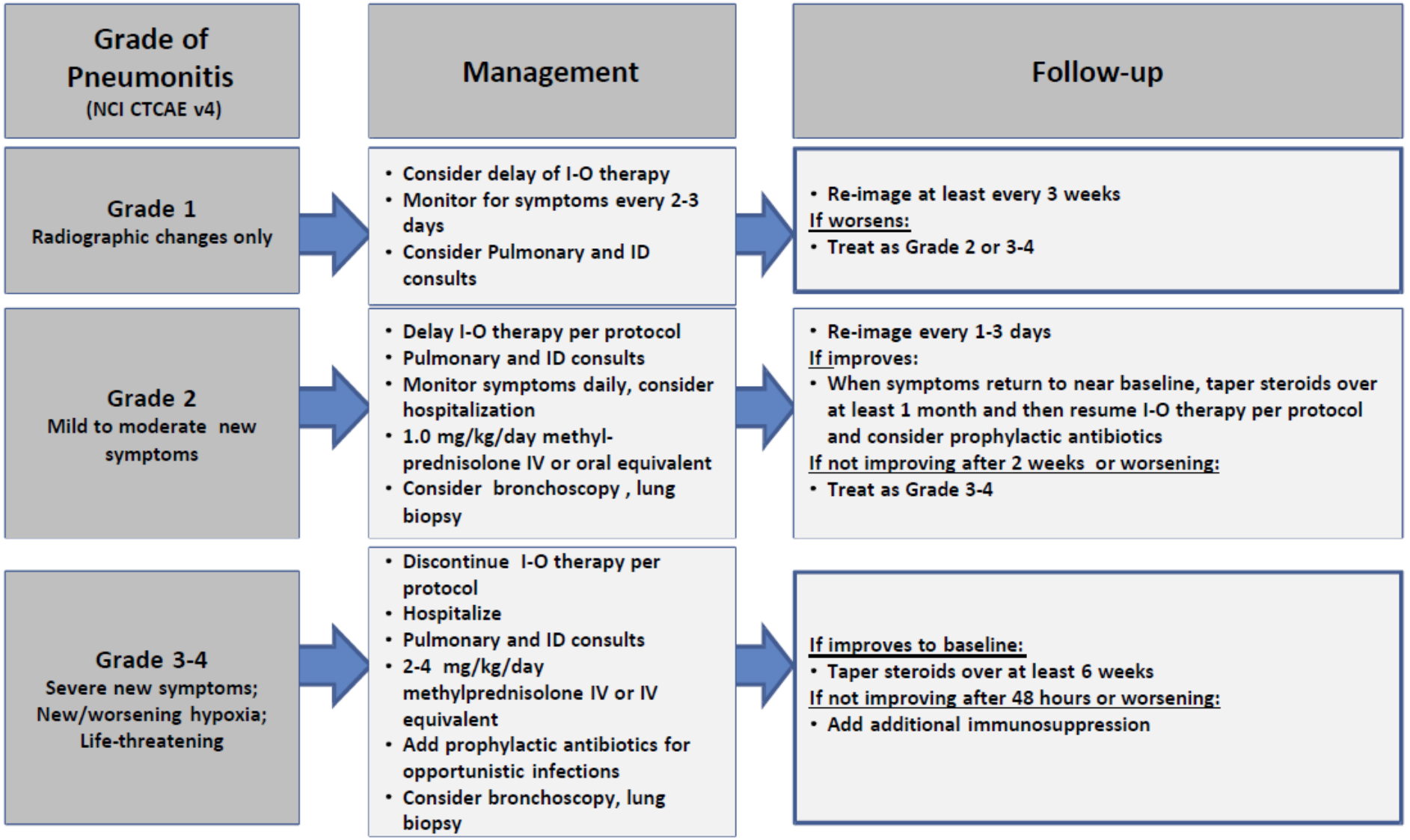
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

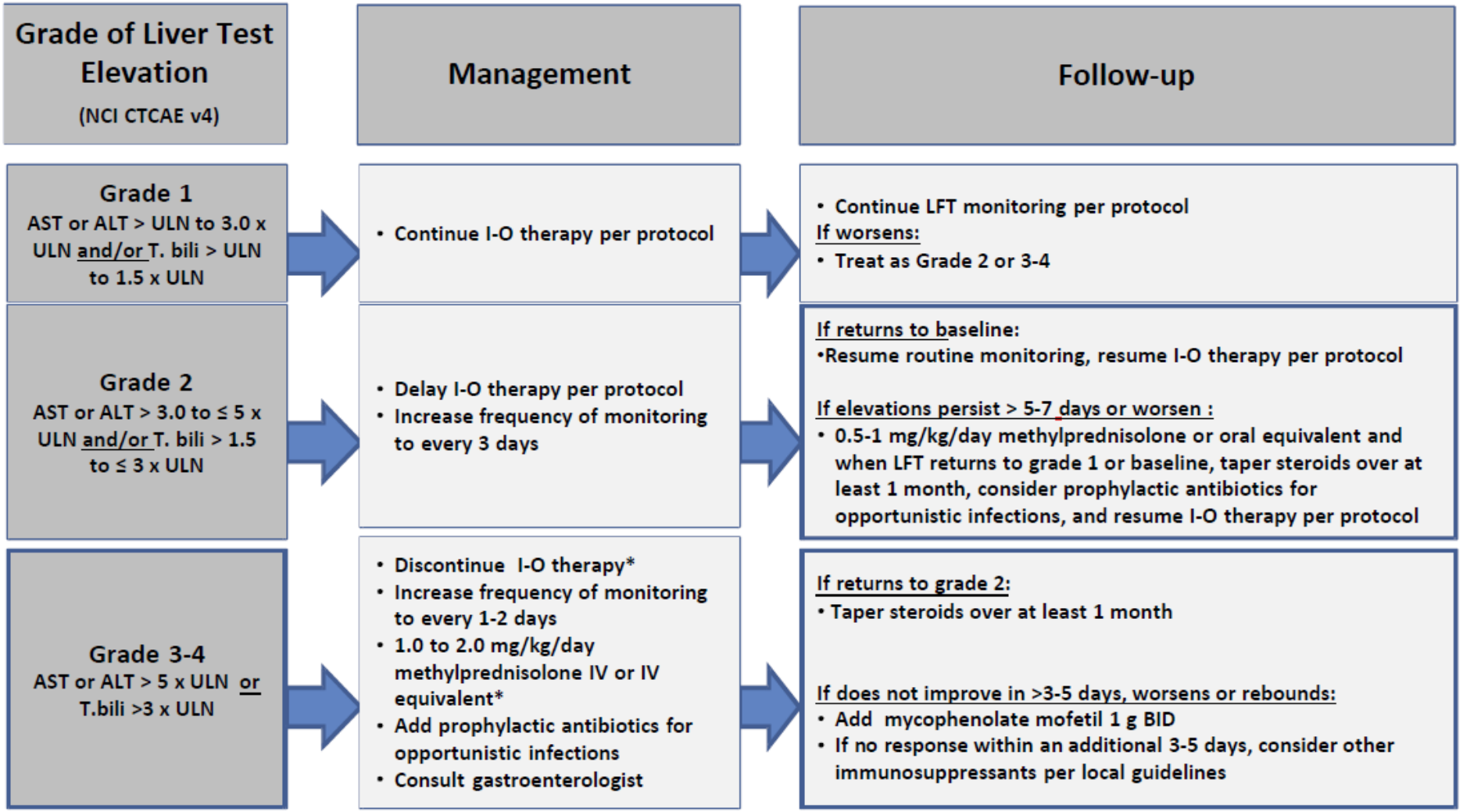
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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.

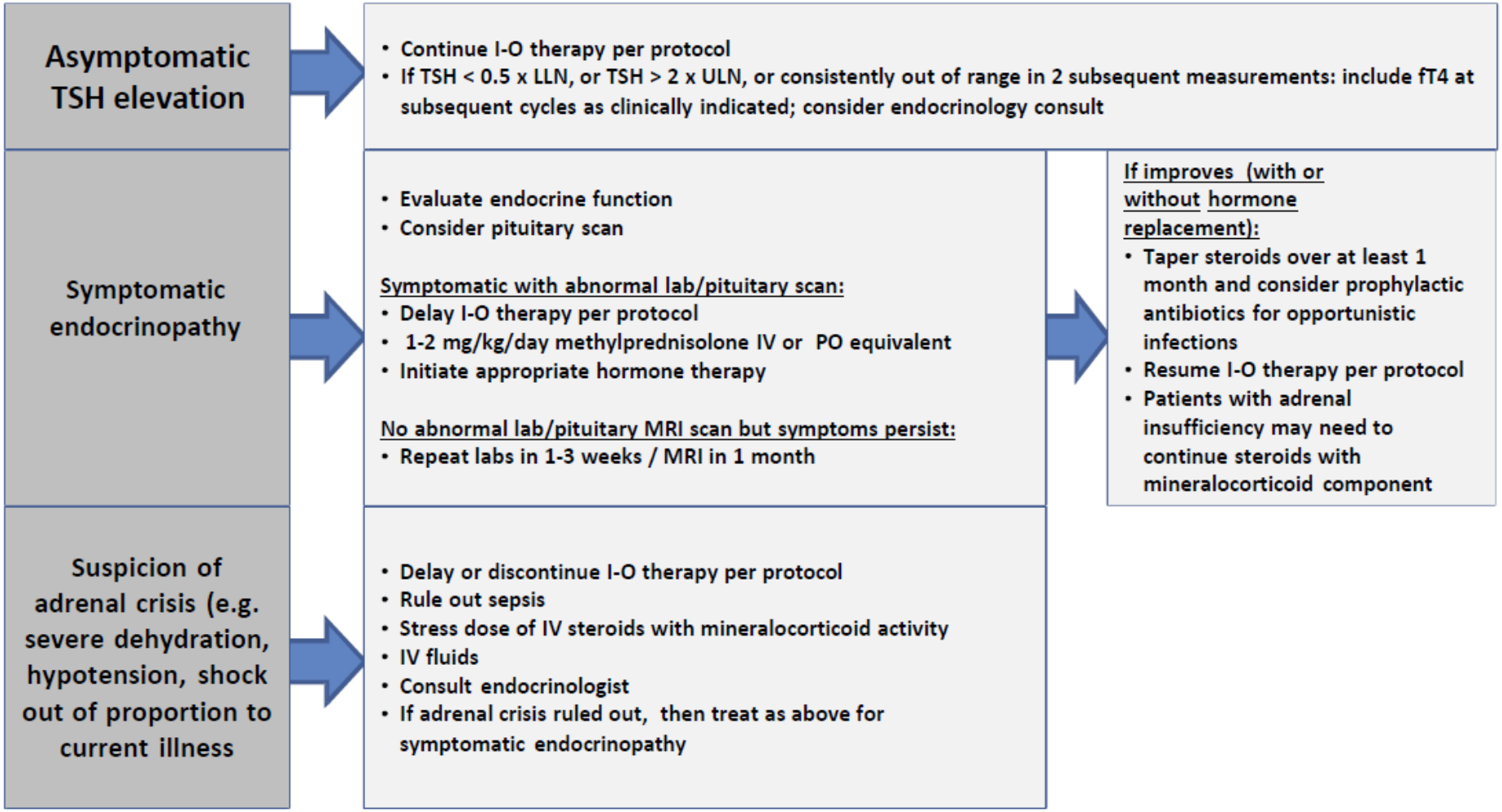


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

Endocrinopathy Adverse Event Management Algorithm

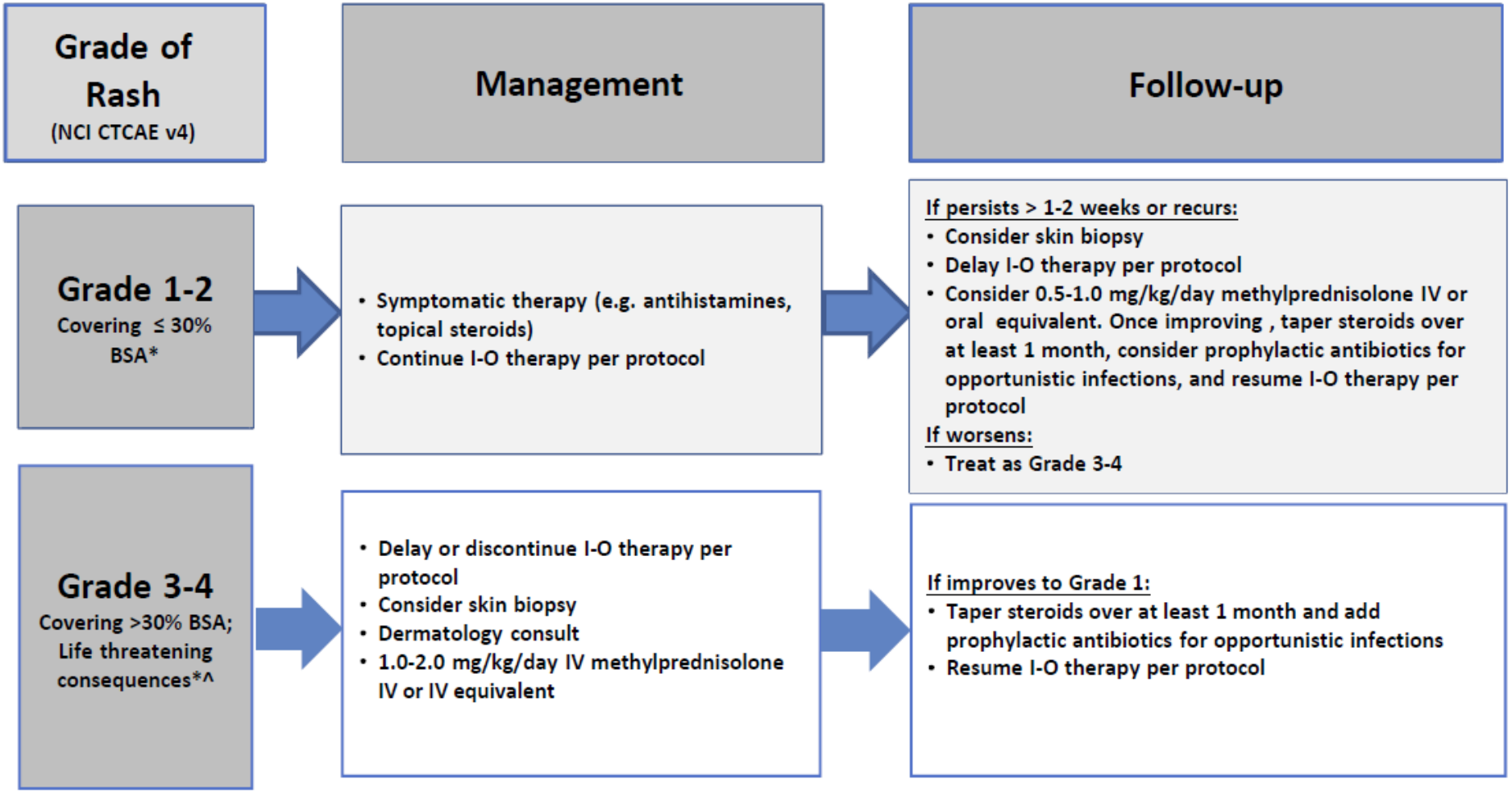
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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.



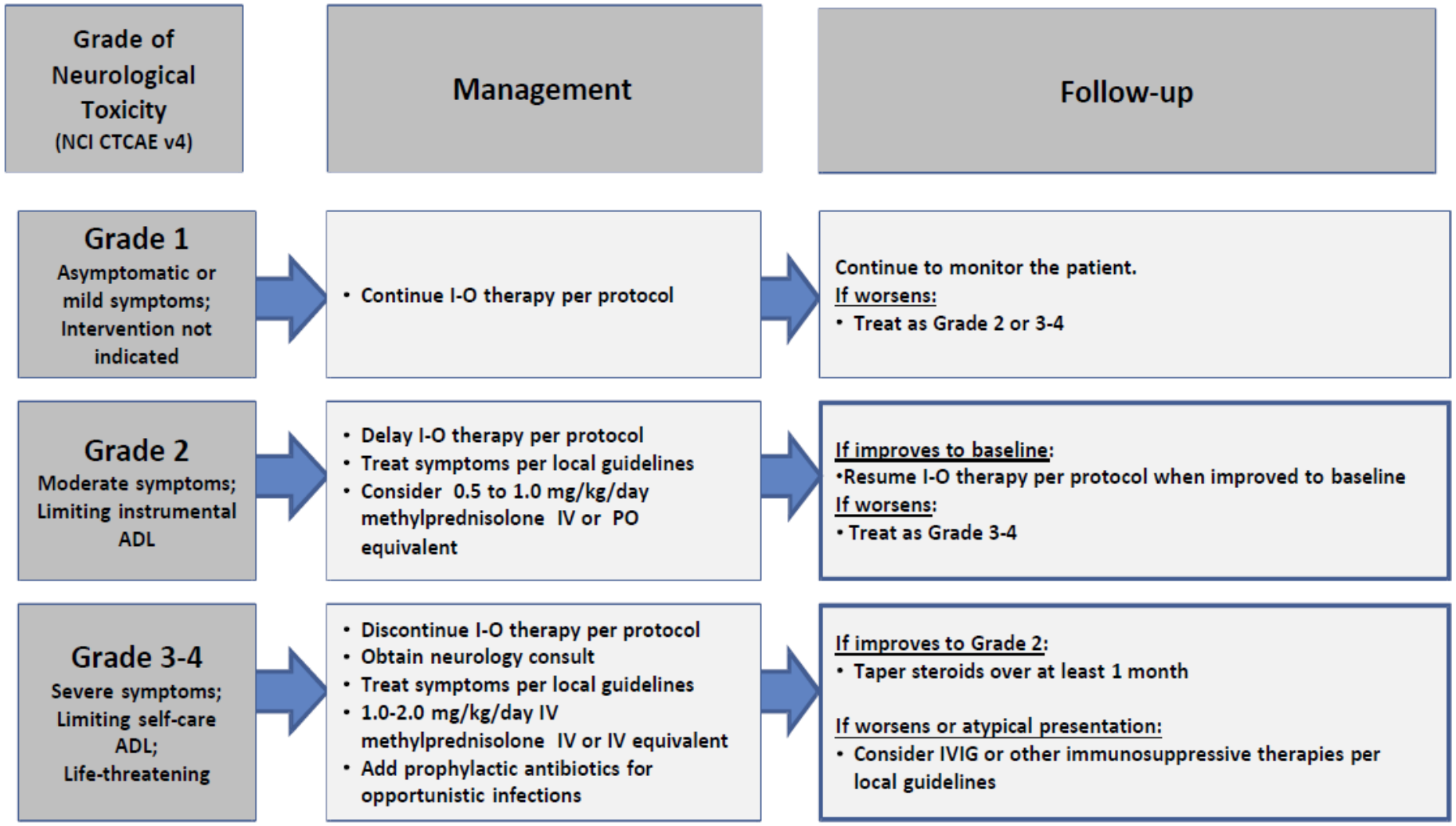
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

10.2 APPENDIX B-2: LISTS OF TERMINOLOGY AND ABBREVIATIONS

10.2.1 List of Terminology

Terminology	Description
Cohort	A group of participants receiving the same immunotherapy combination.
Cohort appendix	A document that guides the treatment of participants in a given cohort. The cohort appendices are identified using a letter designation (eg, Appendix Cohort B).
Core protocol	The master document that provides the elements common across the study and among all cohorts, unless otherwise specified.
Immunotherapy combination	Two or more study interventions administered to a cohort of participants.

10.2.2 List of Abbreviations

Abbreviation	Definition
ADA	anti-drug antibody(ies)
ADP	adenosine diphosphate
AE(s)	adverse event(s)
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AML	acute myeloid leukemia
APC(s)	antigen-presenting cell(s)
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BED	biologically equivalent dose
BUN	blood urea nitrogen
C	cycle
Cavgss	average steady-state concentration
CDX-1401	DEC-201/NY-ESO-1 fusion protein vaccine
cfDNA	cell-free deoxyribonucleic acid
cHL	classical Hodgkin lymphoma
Cmax	maximum observed drug concentration
Cmaxss	maximum steady-state plasma concentration
Cminss	minimum steady-state plasma concentration
Cmin1	trough concentration after the first dose

Abbreviation	Definition
CNS	central nervous system
CRC	colorectal cancer
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DC(s)	dendritic cell(s)
DCR	disease control rate
dMMR	mismatch repair deficient
dsRNA	double-stranded ribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
EPO	erythropoietin
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
Flt3L	FMS-related tyrosine kinase 3 ligand
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
GnRH	gonadotropin-releasing hormone
GU	genitourinary
GVAX	GM-CSF secreting allogenic pancreatic cancer vaccine
Gy	gray
HCC	hepatocellular carcinoma
HIV	human immunodeficiency virus
I/E	inclusion/exclusion
IB	Investigator's Brochure
ICF	informed consent form
IFN	interferon
IgG4	immunoglobulin G4
IM	intramuscular(ly)
iNHL	indolent non-Hodgkin lymphoma
INR	international normalized ratio
irAE(s)	immune-related AE(s)
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IV	intravenous(ly)
LDH	lactate dehydrogenase
mAb	monoclonal antibody
mCRPC	metastatic castration-resistant prostate cancer

Abbreviation	Definition
MSI-H	microsatellite instability-high
MTD	maximum tolerated dose
NCI	National Cancer Institute
NK	natural killer
nmCRPC	nonmetastatic castration-resistant prostate cancer
NSAIDs	nonsteroidal anti-inflammatory drugs
NSCLC	non–small-cell lung cancer
OAS	2'5'oligoadenylate synthetase
ORR	objective response rate
OS	overall survival
PARP	poly ADP ribose polymerase
PBMC(s)	peripheral blood mononuclear cell(s)
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programed cell death ligand 1
PFS	progression-free survival
PI	Principal Investigator
PK	pharmacokinetics
PKR	P68 protein kinase
poly-ICLC	polyinosinic-polycytidylic acid stabilized with polylysine and carboxymethylcellulose
PORTER	Prostate Researching Translational Endpoints Correlated to Response
PPK	population pharmacokinetics
PR	partial response
PSA	prostate-specific antigen
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q3M	every 3 months
Q3W	every 3 weeks
Q4W	every 4 weeks
QD	daily
QoL	quality of life
RBC	red blood cell
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
rhu	recombinant human

Abbreviation	Definition
rhuFlt3L	recombinant human Flt3 ligand
rPFS	radiographic progression-free survival
S	screening
SAC	Safety Assessment Committee
SAE(s)	serious adverse event(s)
SBRT	stereotactic body radiation therapy
SC	subcutaneous(ly)
SCCHN	squamous cell carcinoma of the head and neck
SD	standard deviation
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SJS	Stevens-Johnson syndrome
SOA	Schedule of Activities
TB	tuberculosis
TEN	toxic epidermal necrolysis
Tmax	mean time to maximum serum concentration
TMB	tumor mutational burden
TSH	thyroid stimulating hormone
UC	urothelial carcinoma
ULN	upper limit of normal
US	United States
USPI	US prescribing information
WBC	white blood cell
XRT	radiation therapy

10.3 APPENDIX B-3: APPENDIX COHORT B AMENDMENT HISTORY

DOCUMENT HISTORY	
Documents	**Date of Issue**
Amendment 1	24 Jan 2019
Original Appendix Cohort B	11 Dec 2018

11 REFERENCES

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