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 C

Protocol Number: PICI0033

Amendment Number: 1

Compound Number: CDX-301, INO-5151, Nivolumab

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

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Regulatory Agency Identifying Number(s):

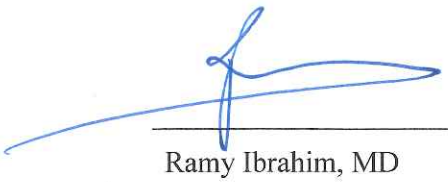
IND NUMBER: 18853

EudraCT NUMBER: Not applicable

Approval Date: Final Protocol: 26 February 2019

Amendment 1: 30 April 2019

SPONSOR APPROVAL PAGE



Date: 09 MAY 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 Practices (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 C

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 (30 April 2019)

Section # and Name	Description of Change
Study Design	
1.2 Schema, Figure 1	Modified to improve identification of key research procedure time points.
1.3 Schedule of Activities	Updated collection schedule for circulating tumor cells and cfDNA to remove complexity in collection timing and amount of material collected from participants.
Study Intervention	
6.6.1 Dose Modifications for CDX-301, INO-5151, and Nivolumab	Added text stating enrollment for the initial 6 participants will be split into 2 groups (of 3 participants each) separated by an 8 week enrollment hold to allow for safety monitoring with this first-in-human combination. Additionally, a second 8 week enrollment hold will follow the second group enrolled to continue monitoring for safety risks before the remaining participants are enrolled.
Clarification of Document	
General Revisions	Document updated to address minor typographical errors and editorial changes for clarity.

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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 C

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 (CDX-301, INO-5151, 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 stimulate antitumor immunity by enhancement of a deoxyribonucleic acid (DNA) vaccination targeting prostate cancer tumor antigens through electroporation (EP), cytokine adjuvants, mobilization and activation of dendritic cells (DCs), and relieving immune suppression of cytotoxic T cells by administration of an anti-programmed cell death 1 (PD-1) monoclonal antibody (mAb) in metastatic castration-resistant prostate cancer (mCRPC):

- Flt-3 ligand (CDX-301) to induce mobilization, activation and/or expansion of DCs
- DNA vaccine INO-5151 encoding human prostate-specific membrane antigen (PSMA), human prostate-specific antigen (PSA), and human interleukin-12 (IL-12) to stimulate antitumor-directed CD8 T-cell responses to castration-resistant prostate cancer (CRPC)-specific tumor antigens
- Anti-PD-1 mAb (nivolumab) to overcome immune suppression of tumoral T cells

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 of INO-5151, CDX-301, and/or nivolumab.	• Sparse PK analysis. • Presence of immune response against PSA and/or PSMA • ADA against CDX-301 and/or nivolumab.

ADA = anti-drug antibodies; IL-12 = interleukin-12; PK = pharmacokinetics; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen

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 CDX-301, INO-5151, and nivolumab as follows:

Intervention	Dose	Frequency	Route	Schedule
CDX-301	75 µg/kg	QD x 5 days x 2 (ie, twice)	SC	Immune-priming Lead-in Days 1-5 and 22-26
INO-5151	3 mg	Immune-priming dose, followed by Q4W x 3 doses, then Q12W	IM followed by EP	Day 8 of Immune-priming Lead-in Starting Day 1 of Cycle 1[a]
Nivolumab	480 mg	Q4W	IV over 30 minutes	Starting Day 1 of Cycle 1

IV = intravenous(ly); IM = intramuscular(ly); EP = electroporation; QD = daily; Q4W = every 4 weeks; Q12W = every 12 weeks; SC = subcutaneous(ly)

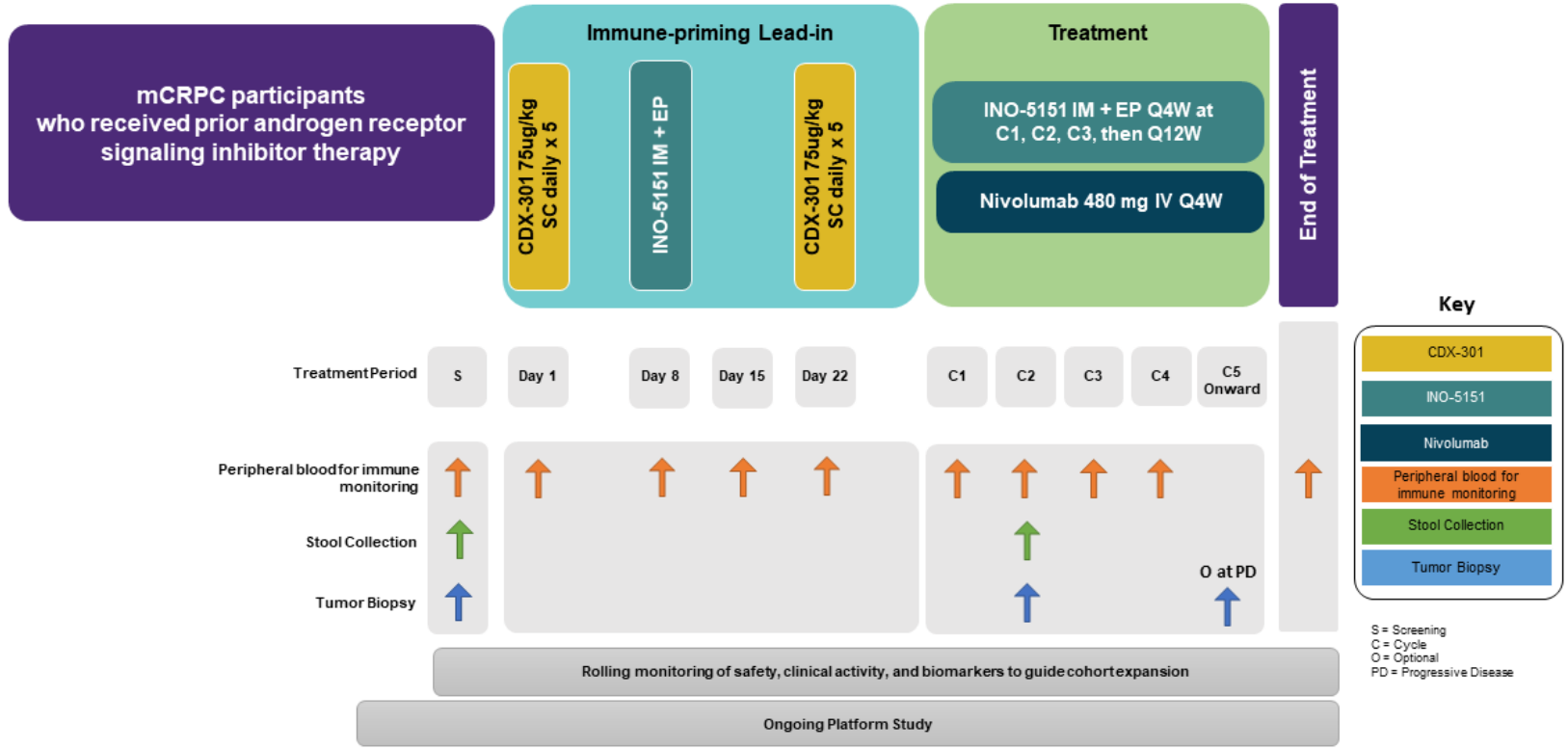
[a] Day 1 of Cycle 1 follows 1 week after Day 22 of the Immune-priming Lead-in

CDX-301 will be administered during the Immune-priming Lead-in only. INO-5151 and 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 1.

Figure 1: Study Schema



EP = electroporation; IM = intramuscularly; IV = intravenously; mCRPC = metastatic castration-resistant prostate cancer; Q4W = every 4 weeks; Q12W = every 12 weeks; SC = subcutaneously

Note: The horizontal axis is not linearly scaled, so the interval for Immune-priming Lead-in appears to be much longer than for the subsequent cycles.

[a] INO-5151 will be administered IM followed by EP.

[b] Day 1 of Cycle 1 follows 1 week after Day 22 of the Immune-priming Lead-in.

CDX-301 will be administered during the Immune-priming Lead-in only. INO-5151 and 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: CDX-301 + INO-5151 + Nivolumab								End of Treatment Visit[c]	Follow up	
		Immune-priming Lead-in				Cycle 1[b] (Q4W)		Cycles 2,3, and 4	Cycle 5 Onward			
Day	Day -28 to Day -1	Days 1 - 5	Day 8	Day 15	Days 22 - 26	Day 1	Day 8	Day 1	Day 1	14 - 28 days after last dose	110 days after last dose	Q3M[d]
Window (days)	-28			± 1	± 1	± 1	± 1	± 3	± 3	± 7	± 10	± 14
Informed consent[e]	X											
Review of I/E criteria	X											
Medical/cancer history	X											
Physical examination	X	X				X		X	X	X		
ECOG performance status	X	X				X		X	X	X	X	
Vital signs (see Core Protocol Section 8.2.3)	X	X				X		X	X	X		
Body weight	X	X	X	X	X	X		X	X (Cycles 5, 8, 11, 14, 17, 20, 23, and 26)	X		
Hematology (see Table 11)	X	X[f] (Day 1)	X[f]	X	X[f] (Day 22)	X[f]	X	X[f]	X[f]	X	X	
Clinical chemistry (see Table 11)	X	X[f] (Day 1)	X[f]	X	X[f] (Day 22)	X[f]	X	X[f]	X[f]	X	X	
Urinalysis	X									X		
Prostate-specific antigen	X	X (Day 1)			X (Day 22)	X		X	X	X	X	
Testosterone level	X											
12-lead ECG	X							X (Cycles 2 and 4)				

Tests & Procedures	Screening/ Enrollment[a]	On-Treatment: CDX-301 + INO-5151 + Nivolumab								End of Treatment Visit[c]	Follow up	
		Immune-priming Lead-in				Cycle 1[b] (Q4W)		Cycles 2,3, and 4	Cycle 5 Onward			
Day	Day -28 to Day -1	Days 1 - 5	Day 8	Day 15	Days 22 - 26	Day 1	Day 8	Day 1	Day 1	14 - 28 days after last dose	110 days after last dose	Q3M[d]
Window (days)	-28			± 1	± 1	± 1	± 1	± 3	± 3	± 7	± 10	± 14
Circulating tumor cells[g]		X[f] (Day 1)				X[f]		X[f]	X[f]	X		
cfDNA (blood)[h]						X[f]		X[f] (Cycles 2, 3, and 4)		X		
Circulating soluble analytes/PK/ADA[i]	X	X[f] (Day 1, Day 5)	X[f]	X[f]	X[f] (Day 26)	X[f]	X[f]	X[f] (Cycles 2, 3, and 4)		X	X	
Blood immune biomarkers[i]	X	X[f] (Day 1, Day 5)	X[f]	X[f]	X[f] (Day 26)	X[f]	X[f]	X[f] (Cycles 2, 3, and 4)		X		
Archival tumor tissue	X											
Tumor biopsy[j]	X							X (Cycle 2)		X (at PD [optional])[j]		
Stool collection[k]	X							X (Cycle 2)[k]				
Concomitant medications	X	X	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[l]											
CDX-301 administration[m]		X			X							
INO-5151 administration[n]			X			X		X (Cycles 2 and 3)	X (Cycles 6, 9, 12, 15, 18, 21, and 24)			

Tests & Procedures	Screening/ Enrollment[a]	On-Treatment: CDX-301 + INO-5151 + Nivolumab								End of Treatment Visit[c]	Follow up	
		Immune-priming Lead-in				Cycle 1[b] (Q4W)		Cycles 2,3, and 4	Cycle 5 Onward			
Day	Day -28 to Day -1	Days 1 - 5	Day 8	Day 15	Days 22 - 26	Day 1	Day 8	Day 1	Day 1	14 - 28 days after last dose	110 days after last dose	Q3M[d]
Window (days)	-28			± 1	± 1	± 1	± 1	± 3	± 3	± 7	± 10	± 14
Nivolumab administration[o]						X		X	X			
Radiographic disease assessment	X							X (prior to Cycle 3)	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; EP = electroporation; I/E = inclusion/exclusion; IV = intravenously; PD = progressive disease; PK = pharmacokinetics; Q3M = every 3 months; Q4W = every 4 weeks; QD = daily; 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] Day 1 of Cycle 1 follows 1 week after Day 22 of the Immune-priming Lead-in.

[c] 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.

[d] 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.

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

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

[g] Circulating tumor cells will be collected at baseline (ie, Day 1 of the Immune-priming Lead-in prior to study intervention administration), Day 1 of each cycle (prior to study intervention administration), and EOT.

[h] cfDNA (blood) will be collected Day 1 of Cycle 1-Cycle 4, and EOT.

[i] Circulating soluble analytes, PK and ADA blood sample, and/or blood immune biomarkers will be collected 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, 15, and 26 of the Immune-priming Lead-in, Days 1 and 8 of Cycle 1, Day 1 of Cycles 2-4, at EOT, and the first follow up visit.

[j] 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.

[k] 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.

[l] 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.

[m] CDX-301 will be administered at a dose of 75 µg/kg subcutaneously (SC) QD x 5 days [ie, Monday – Friday] twice during the Immune-priming Lead-in (Days 1 – 5 and Days 22 – 26).

[n] INO-5151 will be administered at a dose of 3 mg intramuscularly (IM) followed by EP on Day 8 of the Immune-priming Lead-in, Starting with Cycle 1, INO-5151 will be given on the same day as nivolumab on Day 1 of Cycle 1, Cycle 2, and Cycle 3, and every 12 weeks (ie, every 3 cycles) thereafter. A cycle is defined as 4 calendar weeks.

[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. 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). Strategies that mobilize immune cells to the tumor microenvironment, stimulate cytotoxic CD8 T cells to recognize tumor specific antigens, and induce tumor cell killing offer a potential way to extend those benefits.

Deoxyribonucleic acid (DNA) immunization has been recognized as a promising vaccine platform for almost 20 years for a number of reasons (Hokey and Weiner, 2006). Both DNA vaccines and various viral vector vaccines have been explored for diseases where a potent T-cell response may be required to achieve clinical improvement. Prophylactic and therapeutic DNA vaccines have generated immunogenicity that is similar to what has been achieved with viral vectors (Morrow and Weiner, 2010). Potent T-cell immune responses can be generated to virtually any antigenic sequence after antigen processing and presentation. Although traditional live attenuated and viral vector vaccines may also elicit potent T-cell responses, these viral approaches bear safety concerns associated with their vector backbone, which DNA vaccines should and do circumvent. In addition, as opposed to viral-based vaccines which carry a risk of mutation back to a virulent state or spread to unintended individuals, DNA vaccines are not based on an intact natural pathogen and therefore cannot revert to a virulent form. Finally, repeated dosing of viral-based vaccines may be hindered by neutralization of targeted viral vector sequences. The plasmid backbones of DNA vaccines are associated with virtually no immune response, thus allowing repeated dosing to increase or maintain the immune responses

against the DNA encoded antigen over long periods. Additionally, toxicology studies have found no evidence of genome integration as measured by polymerase chain reaction (PCR) in two previous studies of several DNA vaccine products (Sheets et al., 2006a; Sheets et al., 2006b) expressing a variety of inserts, such as human immunodeficiency virus (HIV), Ebola, severe acute respiratory syndrome (SARS), West Nile Virus and malaria antigens (INO-5151/INO-5150 and INO-9012 Investigator's Brochure, 2019). In contrast, pre-existing anti-vector immunity can reduce the immunogenicity and ability to utilize the viral vector for future immunizations. Finally, DNA vaccines are simple and relatively inexpensive to construct, are readily produced in large quantities, and are generally stable for long periods of time. These advantages make DNA-based immunization a desirable immune-based modality for the prevention or treatment of disease.

2.2.1 Background on INO-5151 (PSA, PSMA, Interleukin-12) DNA Delivered via Intramuscular Electroporation (Inovio Pharmaceuticals)

2.2.1.1 PSA and PSMA Immunotherapy

Prostate-specific antigen (PSA) is a protein member of the kallikrein-related peptidase family and is secreted by the epithelial cells of the prostate gland. PSA is present in small quantities in the serum of normal men with healthy prostates, but is often elevated in the presence of prostate cancer or other prostate disorder (Williams et al., 2007). Serum PSA has been utilized as one prostate cancer biomarker in conjunction with other techniques for diagnosis, prognosis, prostate cancer disease recurrence and progression. Previous studies also indicate a role of PSA in the initiation and progression of prostate cancer, making it a potential functional target (Williams et al., 2007).

Prostate specific membrane antigen (PSMA) is a multi-domain protein expressed in either an integral membrane or cytoplasmic form in a variety of cell types, including the neovasculature of several types of solid tumors. Further, PSMA expression is increased in prostate cancer cells as the disease progresses making it a highly relevant target for tumors that are diagnosed later in disease progression rather than earlier (Schmittgen et al, 2003). In a study examining intratumoral PSMA expression in 902 subjects at prostatectomy, Kasperzyk et al. found a positive association between PSMA levels and risk of lethal prostate cancer, which was not independent of the clinical parameters examined, and therefore, did not support the clinical utility of PSMA expression as a biomarker for lethal prostate cancer (Kasperzyk et al., 2013). Much like PSA, previous studies have indicated that PSMA is preferentially expressed in the prostate compared to normal tissues (Cunha et al., 2006). PSMA-specific T cell mediated responses can confer antitumor effects and an increase in the percentage of PSMA-specific T

cells producing interferon gamma (IFN-γ) correlates with clinical improvement in prostate cancer patients (Tjoa et al., 1999; Mincheff et al., 2001).

In contrast to PSA, PSMA expression is more prevalent in extraprostatic tissues (Cunha et al., 2006). PSMA messenger ribonucleic acid (mRNA) and protein expression have been found in both normal tissue and prostate cancer tissue by quantitative PCR and immunohistochemistry, respectively, although the actual levels and location of PSMA expression in normal tissue remain unclear (Cunha et al., 2006; Silver et al., 1997). Despite its reported limited extraprostatic expression, PSMA has also been reported in the brain, duodenum, colon, liver, proximal kidney tubules, and salivary gland (Horoszewicz et al., 1987; Israeli et al., 1994; Lopes et al., 1990; Luthi-Carter et al., 1998; Sácha et al., 2007). Cunha et al. found PSMA mRNA expression in the brain, liver and kidney, although the levels in these organs were approximately 12-18-fold less than the mRNA expression level in the prostate (Cunha et al., 2006). Silver et al. also reported PSMA immunoreactive tissue in prostate epithelium, kidney (luminal site of the proximal renal tubules), duodenum and colon (Silver et al., 1997). This study did not show any PSMA immunoreactivity in the brain as was shown by other groups, and the differentiated prostate tissue expression and over expression of PSMA in metastatic tissues support the study of this unique prostate tumor-associated biomarker for developing new strategies for immune therapy of prostate cancer. Because of its relevance in metastatic prostate cancer, this antigen has been targeted in a variety of both diagnostic evaluations (eg, PSMA positron emission tomography [PET]), as well as therapeutic targets such as antibody drug conjugates (ADC), vaccine therapies, and nanoparticles.

Immunotherapy is a promising approach to develop tumor antigen-specific therapies for prostate cancer (Gulley and Drake, 2011; Troyer et al., 1995; Rice et al., 2008). In antigen-specific approaches, a tumor-associated antigen is directly targeted, either by loading that antigen onto antigen-presenting cells (APC) ex vivo or by incorporating the antigen into a vaccine cellular delivery system at a protein or DNA level. In the absence of immunotherapy, however, T-cell response to tumor antigens such as PSA are difficult to detect in patients, which indicates that some level of pre-existing tolerance may exist (Drake, 2010).

Approximately 1,400 human subjects have been treated or are being enrolled in clinical trials to evaluate immunotherapy based on DNA or viral vectors that encode various prostate-specific antigens (INO-5151/INO-5150 and INO-9012 Investigator's Brochure, 2019). While measurable, anti-prostate tumor-specific immunoglobulin has been difficult to detect, the T-cell antigen-specific activity has been measured somewhat consistently. Measurable tumor responses (National Prostate Cancer Project [NPCP] criteria) to these immunotherapies have also been reported. In general, safety and tolerability has been shown to be acceptable (Drake, 2010; Felici

et al., 2012). Local injection site reactions were the most common safety event observed. Additionally, cellular based vaccines were associated with acceptable systemic safety profile.

In a recently-reported phase 1 study of 62 biochemically recurrent prostate cancer patients, INO-5150 (PSA and PSMA), with and without INO-9012 (interleukin-12 [IL-12] plasmid), was demonstrated to be safe and immunogenic, with observed humoral and cellular responses, including generation of functional antigen-specific CD8 T cells (Shore et al., 2018b). In addition, clinical activity was observed in the form of significantly increased PSA doubling times and reduced percent rise in PSA, which was significantly different in the patients with demonstrated immunogenicity to INO-5150 (Shore et al., 2018a; Shore et al., 2018b).The INO-5151 to be used in this clinical trial is a single-vial combination of INO-5150 and INO-9012, which will facilitate administration.

Refer to the Investigator's Brochure (IB; INO-5151/INO-5150 and INO-9012 Investigator's Brochure, 2019) for additional background information.

2.2.1.2 Interleukin-12 Plasmid with DNA Vaccines

IL-12 is an immune cytokine that is produced by dendritic cells (DCs), macrophage, neutrophils, and B cells in response to antigen stimulation. IL-12 plays an important role in the eliciting effective immune responses through activation of antigen-presenting activity of DCs and promoting the cytotoxic activity of CD8 T cells and natural killer (NK) cells. Thus, IL-12 is an important cytokine in promoting an antitumor immune response. Given its immunomodulatory and additionally anti-angiogenic function, recombinant IL-12 has been evaluated in clinical studies as an anti-cancer agent. A review of clinical applications of recombinant IL-12 lists 17 separate clinical studies conducted in more than 500 patients with advanced solid tumors and various hematologic malignancies (Del Vecchio et al., 2007). Recombinant human IL-12 (rhIL-12) has been evaluated both as monotherapy and in combination with vaccines, other cytokines, or antitumor monoclonal antibodies in these clinical studies. Systemic delivery of rhIL-12 protein can cause significant toxicity (Gollob et al., 2000). In contrast, IL-12 DNA therapy has minimal toxic effects in non-human primates and human subjects (Shore et al., 2018a; Shore et al., 2018b; Schadeck et al., 2006; Boyer et al., 2005; Chong et al., 2007; Kalams et al., 2012; Kalams et al., 2013; Daud et al., 2008). In a recent human trial, the combination of INO-5150 ± INO-9012 was shown to be safe, well tolerated and immunogenic (Shore et al., 2018a; Shore et al., 2018b).

In preclinical studies, use of IL-12 plasmid with DNA vaccines has been shown to substantially increase the immunogenicity of DNA vaccines (Hanlon et al., 2001; Kim et al., 1998a; Kutzler et al., 2005; Operschall et al., 1999; Chattergoon et al., 2004; Egan et al., 2006; Kim et al., 1998b; Calarota and Weiner, 2004; Umemura et al., 2001). Co-administration of cytokine plasmids with DNA vaccines has been studied in rodents (Kim et al., 1997) and have demonstrated a dramatic

increase in specific cytotoxic T-lymphocyte (CTL) activity and provides the basis for evaluation of INO-5151 in the proposed clinical trial. These preclinical studies demonstrated a dramatic increase in specific CTL activity when plasmid DNA was co-administered with an IL-12 plasmid, as compared with results in animals receiving plasmid alone (Chattergoon et al., 2004; Egan et al., 2006; Kim et al., 1998b; Calarota and Weiner, 2004). In summary, DNA vaccine administration in combination with IL-12 DNA has been shown to be generally safe and well tolerated, and possibly more immunogenic, although further studies need to be done (Kalams et al., 2013).

2.2.1.3 Rationale for Use of Electroporation

Several groups are developing methods to improve the immune responses of DNA vaccines using genetic optimization (including use of highly concentrated DNA formulations, multiple ribonucleic acid (RNA) optimizations and addition of improved leader sequences), cytokine adjuvants, and alternative cellular delivery (ie, electroporation [EP]) (Kutzler and Weiner, 2008). The approach being studied in this trial employs all these methods with delivery of IL-12 as an immune cytokine and an emphasis on improving the transfection of DNA using EP. EP is the application of a localized electrical field at the site of injection to facilitate cell uptake of DNA by permeabilizing cell membranes and may also induce local inflammation (Kutzler and Weiner, 2008; Sardesai and Weiner, 2011). This physical process exposes the target tissue to a brief electric field pulse that induces temporary and reversible pores in the cell membrane to enhance the cellular uptake of large molecules such as DNA. By temporarily increasing the permeability of cell membranes, EP has been shown to be an efficient way to introduce DNA into cells (Aihara and Miyazaki, 1998; Gehl and Mir, 1999) and to increase the expression level of antigens encoded by DNA (Hirao et al., 2008). The EP technology has been used for more than three decades by molecular biologists for in vitro cell transfection. Clinical applications of EP have been used in human studies of gene therapy and more recently in cancer (Sardesai and Weiner, 2011).

The hypothesis is that EP will increase the uptake and expression of plasmid DNA (pDNA), generating significantly increased immunogenicity. Electroporation enhances both cellular and humoral immune responses, using less DNA than intramuscular immunizations alone (Schoenly and Weiner, 2008). Studies have demonstrated the ability of EP to augment specific cellular immune responses in mice (Liu et al., 2008) and in macaques (Luckay et al., 2007). Luckay et al. found that delivering simian immunodeficiency virus (SIV) DNA vaccines intramuscularly (IM) followed by EP increased the potency of these vaccines 50-200 fold (Luckay et al., 2007). There are various means of delivering EP (ie, constant current vs. constant voltage) and testing these strategies in mice and pigs has shown a constant current device may be the most effective at generating immune responses (Draghia-Akli et al., 2008). Studies in macaques found that EP of

SIV DNA + IL-12 plasmids yielded 10-fold higher responses than DNA injections without EP (Hirao et al., 2008), and that this immune response was boosted with additional doses. The magnitude of achievable responses is similar to that seen with natural SIV infection, in the order of 10,000 spot forming units (SFU)/million peripheral blood mononuclear cells (PBMC) in an enzyme-linked immunospot (ELISpot) assay. These responses are also polyfunctional, as defined by the ability of immune cells from treated animals to generate IFN-γ, tumor necrosis factor alpha (TNF-α) and interleukin-2. Furthermore, the functional consequence of EP delivery of DNA encoding an antigen in combination with IL-12 includes an improved ability of specific CD8+ T-cells to proliferate in cell culture in response to antigenic stimulation compared to delivery without EP (Hirao et al., 2008).

As of 30-Jun-2018, 3,319 doses had been administered to 1,096 subjects via the CELLECTRA® 2000 by either IM or intradermal administration. Among subjects who received PSA, PSMA, and plasmids with a DNA backbone identical to that of INO-5150 and delivered IM followed by EP alone or in combination with IL-12 plasmid DNA (eg, INO-9012), the most commonly reported adverse event reported was injection site pain (Table 2).

Table 2 Adverse Events Reported in Studies of Inovio DNA Delivered IM with Electroporation Occurring in at Least 5% of Subjects

Adverse Event Preferred Term	Number of Subjects (%) (N = 1022)
Injection site pain	570 (55.8)
Fatigue	228 (22.3)
Injection site erythema	190 (18.6)
Headache	187 (18.3)
Myalgia	148 (14.5)
Upper respiratory tract infection	130 (12.7)
Injection site swelling	128 (12.5)
Injection site pruritus	110 (10.8)
Nausea	110 (10.8)
Arthralgia	89 (8.7)
Injection site bruising	81 (7.9)
Malaise	76 (7.4)

Source: INO-5151/INO-5150 and INO-9012 Investigator's Brochure, 2019

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 preclinical 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). Preclinical models have also shown that Flt3L administration can enhance the antitumor immunity of checkpoint inhibitors such as PD-1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies to promote tumor regression of non-immunogenic tumors (Lynch et al., 1997).

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 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. 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. Furthermore, mobilization of DCs by administration of Flt3L followed by exposure to IL-12, PSA, and PSMA may lead to improved activation of DCs and antigen presentation for eliciting a robust antitumor immune response to vaccination with tumor antigens.

Refer to the 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 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 non-small cell lung cancer (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 advanced mCRPC. This is consistent with mCRPC having a low level of immune cell infiltrate and tumor mutational burden (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 [nivolumb] US Prescribing Information [USPI], 2018) for detailed background information on nivolumab.

2.2.4 Rationale for CDX-301 + INO-5151 + Nivolumab Immunotherapy Combination

This study cohort is designed to explore a multi-pronged approach to stimulate antitumor immunity by enhancement of a DNA vaccination targeting prostate cancer tumor antigens through EP, cytokine adjuvants, mobilization and activation of DCs, and relieving immune

suppression of cytotoxic T cells by administration of an anti-PD-1 monoclonal antibody (mAb) in mCRPC:

- Flt3L (CDX-301) to induce mobilization, activation, and/or expansion of DCs
- DNA vaccine INO-5151 for expression of human PSMA, PSA, and IL-12 to stimulate antitumor directed CD8 T-cell responses to CRPC-specific tumor antigens
- Anti-PD-1 mAb (nivolumab) to overcome immune suppression of tumoral T cells

Flt3L binds CD135 (Flt3 receptor) and induces proliferation, differentiation, and mobilization of hematopoietic stem cells, early progenitor cells, and DCs. Flt3L is a key regulator of DCs, inducing marked increases and activation of both myeloid and plasmacytoid DCs. Immunologic analyses have shown 10 to 100+ fold increase in DCs (including CD141+ DCs), as well as augmentation of humoral and cellular responses to the NY-ESO-1 vaccine; however, no clear activity as monotherapy was noted in patients with advanced cancer (Ohri et al., 2018), suggesting CDX-301 promotes antitumor immunity but not sufficiently to result in clinical benefit. These observations suggest that combination of CDX-301 with immunotherapies generating effective CD8 T cell responses, such as INO-5151, may lead to an effective antitumor response, specifically in the presence of a checkpoint inhibitor. The combination of CDX-301, which increases innate immune cells, with a DNA-encoding vaccine and immune-stimulatory cytokine IL-12 is hypothesized to induce potent antitumor immunity (Shore et al., 2018a; Schadeck et al., 2006; Boyer et al., 2005; Chong et al., 2007; Kalams et al., 2012; Kalams et al., 2013; Daud et al., 2008; Gollob et al., 2000; Bhardwaj et al., 2016, Gao et al., 2018). A 29-fold increase in DCs was seen at Day 15 in a trial of CDX-301 in nmCRPC, which support the rationale for this agent in the immune-priming period prior to vaccination. INO-5151 is a DNA based vaccine encoding PSA and PSMA, 2 antigens that are widely expressed in advanced prostate cancer and also encodes IL-12, an adjuvant cytokine with preclinical and clinical data supporting that it increases CD8 T cell responses (Shore et al., 2018a; Shore et al., 2018b). These plasmids will be administered IM followed by EP to enhance cellular uptake of DNA and increase potency. In a recently reported phase 1 study in patients with non-metastatic biochemically recurrent prostate cancer, INO-5150, with and without INO-9012, was safe and immunogenic with demonstrated clinical activity (Shore et al., 2018a; Shore et al., 2018b). The majority of patients experienced a slowing of pre-treatment PSA doubling times (a reflection of disease activity). Patients who experienced disease stabilization by Week 27 continued to Week 72, and importantly, this trend was seen in those with a pre-study PSA doubling time (DT) of < 6 months. PSA DT of < 6 months in a biochemically recurrent population are associated with a worse prognosis and greater likelihood of developing overt metastatic disease. The final component of this regimen, nivolumab, an anti-PD-1 agent, will be given as systemic therapy to

target adaptive resistance pathways and provide ongoing immune stimulation throughout the vaccine regimen cycle.

Further, ongoing clinical studies support this combination approach. The combination of vaccines and anti-PD-(L)1 therapy is being assessed in ongoing studies in several tumor types, including SCCHN, glioblastoma, UC, and human papillomavirus cancers (Table 3). CDX-301, in combination with a vaccine (CDX-1401) and polyinosinic-polycytidylic acid stabilized with polylysine and carboxymethylcellulose (poly-ICLC), has been studied in patients with melanoma (Table 3). 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).

While each component is unlikely to yield clinical benefit on its own in mCRPC, these individual components (CDX-301, INO-5151, and nivolumab) provide different mechanisms to target and enhance immunogenicity by activating innate and adaptive immune mechanisms in order to elicit an antitumor immune response.

Table 3: Clinical Studies Supporting the Co-administration of Components of this Study Intervention

Study	Disease Site	N	Combination	Findings
Vaccine + Anti-PD-(L)1 Combinations				
NCT03162224	SCCHN (HPV associated)	50	MEDI0457 (INO-3112) vaccine + durvalumab	Single arm, open-label study ongoing to assess safety and tolerability, antitumor activity (ORR, PFS, DCR, OS), and immunogenicity.
NCT03439085	HPV cancers	77	MEDI0457 (INO-3112) vaccine + durvalumab	Non-randomized, parallel assignment, open-label study to assess efficacy (ORR, PFS, DCR, OS) and safety.
NCT03491683	Glioblastoma	52	INO-5401 + INO-9012 vaccine + cemiplimab + XRT + temozolomide (if clinically indicated)	Non-randomized, parallel assignment, open-label study ongoing to assess safety, immunogenicity, and preliminary efficacy (OS).
NCT03502785	UC	85	INO-5401 + INO-2012 vaccine + atezolizumab	Non-randomized, parallel assignment, open-label study ongoing to assess safety, immunogenicity, and preliminary efficacy (ORR, DoR, PFS, OS).
Vaccine + CDX-301 Combinations				
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)

CDX-1401 = DEC-201/NY-ESO-1 fusion protein vaccine; DC = dendritic cell; DCR = disease control rate; DoR = duration of response; Flt3L = FMS-related tyrosine kinase 3 ligand; HPV = human papillomavirus; NK = natural killer; ORR = objective response rate; OS = overall survival; PBMC = peripheral blood mononuclear cell; PD-(L)1 = programmed cell death 1 or anti-programmed cell death ligand 1; PFS = progression-free survival; poly-ICLC = polyinosinic-polycytidylic acid stabilized with polylysine and carboxymethylcellulose; SCCHN = squamous cell carcinoma of the head and neck; UC = urothelial carcinoma; 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, CDX-301, INO-5151, and nivolumab); however, the combination has not been previously studied in animal models or in human studies. Each component has been studied specifically in prostate cancer and was well tolerated (Higano et al., 2004; Brahmer et al., 2010; Topalian et al., 2012; Shore et al., 2018a; Shore et al., 2018b). 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 OS as compared with the current standard of care in subjects with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or SCCHN.

The monotherapy 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 of 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).

INO-5151

DNA vaccines are simple and relatively inexpensive to construct, are readily produced in large quantities, and are generally stable for long periods of time, making them a desirable immune-based modality for the prevention or treatment of disease. Additionally, nonclinical studies have demonstrated no evidence of genome integration as measured by PCR in 2 previous studies of several DNA vaccine products expressing a variety of inserts (INO-5151/INO-5150 and INO-9012 Investigator's Brochure, 2019). In contrast, pre-existing anti-vector immunity can reduce immunogenicity and ability to utilize the viral vector for future immunizations.

The plasmid backbones of DNA vaccines are associated with limited, if any, immune response, allowing repeated dosing to increase or maintain immune responses over long periods. Repeated dosing of viral-based vaccines may be hindered by neutralization of targeted viral vector sequences. As opposed to viral-based vaccines, which carry a risk of mutation back to a virulent state or spread to unintended individuals, DNA vaccines are not based on an intact natural pathogen, and therefore, cannot revert to a virulent form.

The combined safety data from completed and ongoing trials with IL-12 plasmid DNA have demonstrated that there have been no significant safety concerns identified in the studies in which IL-12 (eg, INO-9012) is used as an adjuvant in combination with other plasmids. In addition, up to 5.8 mg of IL-12 DNA has been administered intratumorally followed by EP, and no safety signals were observed.

In contrast to high-dose intravenous (IV) recombinant human IL-12 protein, IL-12 plasmid DNA has showed an acceptable safety profile in clinical studies when delivered intramuscularly either alone or when followed by EP. The use of IL-12 DNA has also been associated with expansion of antigen-specific IFN-γ positive effector cells, as well as granzyme B production. The induced immunity included both a CD8+ as well a CD4+ component.

The most frequently reported AEs across studies in which PSA, PSMA and plasmids with a DNA backbone identical to that of INO-5150 and delivered via IM+EP alone or in combination with IL-12 plasmid DNA (eg, INO-9012) are provided in Table 2. Injection site pain was the most frequently reported treatment-related AE across all studies. There were few treatment-related Grade 3 or Grade 4 AEs or serious adverse events (SAEs).

These data indicate that synthetic consensus antigenic sequences inserted into the plasmid backbone generate significant cellular and humoral immune responses, without compromising the acceptable safety profile of naked DNA delivery (Doukas et al., 2011; Ledwith et al., 2000). The generally acceptable benefit/risk profile of DNA vaccines delivered using EP supports further study in selected diseases, such as prostate cancer.

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. CDX-301 administered in combination with vaccines was well tolerated, without SAEs, and promoted integrated immunity (Bhardwaj et al., 2016). 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).

CDX-301, INO-5151, and Nivolumab

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 4.

Table 4: Cohort-Specific Objectives and Corresponding Endpoints

Objectives	Endpoints
Primary	
• To determine the safety of CDX-301 + INO-5151 followed by INO-5151 + nivolumab in participants with mCRPC.	Refer to the core protocol.
Secondary	
• To determine the ORR of CDX-301 + INO-5151 + nivolumab in participants with measurable mCRPC. • To determine the DCR ≥ 9 months of CDX-301 + INO-5151 + nivolumab in participants with measurable mCRPC. • To evaluate the rPFS of CDX-301 + INO-5151 + nivolumab in participants with mCRPC. • To estimate the OS of CDX-301 + INO-5151 + 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 of INO-5151, CDX-301, and/or nivolumab. Refer to the core protocol for overall exploratory objective(s).	• Sparse PK analysis. • Presence of immune response against PSA and/or PSMA • 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 immune profiles, including dendritic cells.

ADA = anti-drug antibodies; DCR = disease control rate; IL-12 = interleukin-12; mCRPC = metastatic castration-resistant prostate cancer; ORR = objective response rate; OS = overall survival; PK = pharmacokinetics;

PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; rPFS = radiographic progression-free survival

4 STUDY DESIGN

4.1 OVERALL DESIGN

In this study intervention cohort, INO-5151 and CDX-301 will be administered during the Immune-priming Lead-in. CDX-301 will be administered on Days 1-5 and Days 22-26 and INO-5151 will be administered on Day 8 of the Immune-priming Lead-in. Thereafter, INO-5151 will be administered in Cycle 1, Cycle 2, and Cycle 3 and every 12 weeks (Q12W; ie, every 3 cycles) thereafter for up to 2 years, concurrent with nivolumab. Nivolumab will be administered every 4 weeks (Q4W) starting in Cycle 1 for up to 2 years (Figure 1), 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 INO-5151 and nivolumab are administered on the same day is: INO-5151 via EP followed by nivolumab infusion.

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 nivolumab (ie, Cycle 2). 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 2.2.4.

4.3 JUSTIFICATION FOR DOSE

The doses of INO-5151 and CDX-301 proposed for this study have 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).

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, there does not appear to be overlapping toxicities. Therefore, the combination of CDX-301, INO-5151, and nivolumab at the doses proposed is considered warranted for the evaluation of safety and clinical activity 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 INO-5151 Dose and Schedule

INO-5151 will be administered at a dose of 3 mg followed by EP in Immune-priming Lead-in, followed by 3 doses administered Q4W starting at Cycle 1, and then Q12W thereafter. Administration of INO-5151 will commence on Day 8 of the Immune-priming Lead-in, based on doses studied in the phase 1 clinical study (PCa-001) and a schedule that has been modified to Q4W by the inclusion of a dose at Cycle 2. The PCa-001 study which assessed the safety, tolerability, and antigen-specific immune responses of INO-5150 with or without INO-9012 delivered via IM EP at 2 doses of INO-5150 (high-dose: 8.5 mg or low-dose: 2 mg) alone or in combination with INO-9012 1 mg in patients with prostate cancer (INO-5151/INO-5150 and INO-9012 Investigator's Brochure, 2019). The doses selected for Study PCa-001 were based on previous human experience with other DNA vaccines and preclinical data with INO-5150 and INO-9012. A total dose of 8.5 mg INO-5150 DNA was selected for Study PCa-001 based on the safety and immunogenicity data generated in Studies HPV-001 and FLU-001, where 6 mg of DNA were delivered via IM+EP, which showed trends toward higher response rates and magnitudes of IFN-γ ELISpot responses in the high dose cohort compared to the low (0.6 mg) and mid-dose (2 mg) cohorts without significant safety issues (INO-5151/INO-5150 and INO-9012 Investigator's Brochure, 2019). In combination with INO-9012 1 mg (ie, the same dose equivalent of INO-9012 proposed for this study), the mid-dose of 2 mg proved effective at generating an immune response (Shore et al., 2017).

Grade 1 – 3 AEs were reported in 82% of the 62 patients enrolled in study PCa-001, including 75% treated with low-dose INO-5150 and 87% treated with low-dose INO-5150 in combination with INO-9012. Common AEs included injection site pain, swelling, and erythema, all of which were Grade 1 – 2. Grade 3 SAEs of presyncope, cardiac disorder, fall, neoplasm, and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation occurred in 5 patients, and none were considered treatment-related; there were no Grade 4 or 5 SAEs (Shore et al., 2017).

Among the 61 evaluable patients across the 4 cohorts in study PCa-001, 77% demonstrated T cell immunogenicity, 60% had IFN-γ reactivity by ELISpot, 10% and 8% had antibody titers against PSA and PSMA, respectively, and 38% exhibited CD38, perforin + CD8 T cell responses. A clinical effect was demonstrated by evidence of dampening of the percent rise in PSA and increased PSA doubling times in the majority of patients (Shore et al., 2018a; Shore et al., 2018b).

4.3.3 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).

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, 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.

4.4 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 $\geq$ 1,500/mm^3 without growth factor support (within < 28 days of assessment)
    c. Platelet count $\geq$ 100,000/mm^3
    d. Estimated glomerular filtration rate (GFR) $\geq$ 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. No known histologic evidence of neuroendocrine differentiation or small cell histology.

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 had prior cancer vaccine therapy.
3. Has a history of acute myeloid leukemia (AML).
4. History of unstable or deteriorating cardiac disease within the previous 6 months prior to screening including but not limited to the following:
    a. Unstable angina or myocardial infarction
    b. Congestive heart failure (New York Heart Association [NYHA] Class III or IV)
    c. Uncontrolled clinically significant arrhythmias
5. Any pre-excitation syndromes (eg, Wolff-Parkinson-White syndrome).

5.3 LIFESTYLE CONSIDERATIONS

No lifestyle considerations/restrictions are required for this cohort.

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 5.

Table 5: Study Intervention

Study Intervention Name	Dosage Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Sourcing
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
INO-5151	Single-use vial containing pGX1101 (plasmid encoding PSA; INO-5101), pGX1108 (plasmid encoding PSMA; INO-5108), and pGX6001 (plasmid encoding IL-12) (1:1:1 ratio w/w) in 1x SSC, pH 7 for injection	3 mg/mL	3 mg	IM followed by EP	Inovio Pharmaceuticals
Nivolumab	Aqueous solution	10 mg/mL	480 mg	IV infusion	Bristol-Myers Squibb

EP = electroporation; IL-12 = interleukin-12; IM = intramuscular(ly); IV = intravenous(ly); PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; SC = subcutaneous(ly); SSC = Saline Sodium Citrate formulation

The preferred sequence when INO-5151 and nivolumab are administered on the same day (eg, Day 1 of Cycle 1) is: INO-5151 via electroporation (EP) followed by infusion of nivolumab. Study intervention will be administered as follows:

- CDX-301 will be administered only during the Immune-priming Lead-in at a dose of 75 µg/kg SC QD x 5 days (Immune-priming Lead-in Days 1 – 5 and Days 22 – 26 [ie, Monday – Friday on the weeks administered]).
- INO-5151 will be administered intramuscularly (IM) at a dose of 3 mg followed by EP (Section 6.1.1) on Day 8 of the Immune-priming Lead-in, Day 1 of Cycles 1, 2, and 3, and every 12 weeks thereafter (ie, Cycles 6, 9, 12, etc. for up to 2 years) on the same day as nivolumab.
- 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.

  Note: Day 1 of Cycle 1 follows 1 week after Day 22 of the Immune-priming Lead-in. 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.

6.1.1 Investigational Device

The CELLECTRA® 2000 device is intended for the enhanced uptake and expression of plasmid DNA-based biologics in order to enhance vaccine efficacy (ie, via EP). The system is battery powered and includes a pulse generator, applicator, and disposable sterile needle array. The plasmid is delivered manually by IM injection. All device components are designed to fulfill international standards, where applicable, and manufactured in accordance to Inovio design and quality specifications.

CELLECTRA® 2000 generates minimally-controlled, pulsed electrical currents that temporarily and reversibly increase cellular membrane permeability without damaging the tissue. An injected plasmid DNA formulation can be introduced into the cells with enhanced uptake during the period of increased permeability.

Refer to the IB (INO-5151/INO-5150 and INO-9012 Investigator's Brochure, 2019) and the CELLECTRA® 2000 User's Manual for complete information and instructions on the use of this device.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

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

INO-5151 should be stored in a secure, locked area at 2-8°C.

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.

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 CDX-301, INO-5151, and Nivolumab

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

An 8-week enrollment hold will be implemented following treatment of the first 3 participants in order to monitor for acute and sub-acute adverse events and ensure that no unanticipated safety risks are identified. If no unanticipated safety risks are identified, 3 additional participants may be enrolled and initiated on study intervention. After treatment of the 6th participant, another 8-week enrollment hold will be implemented. During this enrollment hold, new participants may be consented and screened, but not initiated on study intervention.

The initial 6 participants treated in this cohort will be observed for the occurrence of any of the AEs described in Table 6 that are observed from the beginning of treatment through completion of the first cycle of nivolumab (ie, 8 weeks) and that are considered by the Investigator to be possibly, probably, or definitely related to CDX-301, INO-5151, nivolumab, or the immunotherapy combination, unless there is a clear alternative explanation. If 1 or no AEs described in Table 6 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 6 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 6 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 6 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

CDX-301, INO-5151, or nivolumab in this study. If an Investigator believes a toxicity is uniquely related to one agent drug, then appropriate documentation is required regarding the drug to which the Investigator is attributing the AE. The following retreatment requirements will apply:

- During the Immune-priming Lead-in if, in the opinion of the Investigator, the toxicity is related to CDX-301, then CDX-301 should be withheld (eg, skipped) according to recommended dose modifications.
    - If CDX-301-related toxicities prevent the administration of CDX-301 on Days 22 – 26, administration may be held for up to 1 week to allow for recovery.
- Cycle 1 may commence following the completion of the Immune-priming Lead-in provided the participant meets the retreatment criteria for INO-5151.
    - Starting with Cycle 1 if, in the opinion of the Investigator, the toxicity is related to INO-5151 and/or nivolumab then both drugs should be held according to recommended dose modifications. 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, unless written approval to restart therapy is provided by the Medical Monitor.

The anticipated important safety risks associated with the administration of CDX-301, INO-5151, and/or nivolumab, as well as the measures to be taken, are outlined in the following sections. Refer to the Investigator's Brochures for CDX-301, INO-5151, and nivolumab for complete summaries of safety information.

Table 6: 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 CDX-301, INO-5151, nivolumab, 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 CDX-301, INO-5151, and Nivolumab

In general, the toxicities associated with the monotherapy administration of CDX-301, INO-5151, and nivolumab 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.

The most common toxicity reported with the administration of INO-5151 has been mild to moderate administration site pain, which often resolves spontaneously within 5 to 10 minutes and may be accompanied by swelling and erythema. Evaluation of creatine phosphokinase for risk of muscle damage and electrocardiogram for risk of cardiac conduction abnormalities has been clinically unremarkable, and no EP-related safety issues have been identified other than transient injection site pain as mentioned above.

In human studies to date, rhuFlt3L 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. When administered in combination with CDX-1401, a DEC-201/NY-ESO-1 fusion protein, treatment was well tolerated, with the most commonly reported AEs being Grade 1-2 chills, injection site erythema and pain, fever, and myalgias.

6.6.1.2 Dose Modifications and Toxicity Management for Adverse Events Associated with CDX-301, INO-5151, and Nivolumab

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 C-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, INO-5151, 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 7.

Table 7: Dose Modification and Toxicity Management Guidelines for Infusion/Injection-related Reactions Associated with the Administration of CDX-301, INO-5151, 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 related to the study intervention, and not related to electroporation, despite adequate premedication should be permanently discontinued from further study intervention**	Participant may be premedicated according to local treatment guidelines
Grades 3 or 4 Grade 3: 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) Grade 4: 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 CDX-301, INO-5151, and Nivolumab

Dose delays and interruptions are permitted for toxicity reasons (see Section 6.6.2, 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.

Appropriate documentation is required regarding the drug 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.

6.6.2 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 after the last dose, the participant must discontinue study intervention, 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 8.

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 8.

Table 8: 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
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]

Adverse Reaction	Severity[a]	Dose Modifications
	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.

6.6.3 Dose Modifications for INO-5151

Dose modifications of INO-5151 will not be allowed in this study. 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 discontinue the combination therapy, unless written approval to restart therapy is provided by the Medical Monitor.

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 that are withheld (eg, skipped) for toxicity attributed to CDX-301 (Table 9), and doses that are skipped should not be made up. If CDX-301-related toxicities prevent the administration of CDX-301 on Days 22 – 26 of the Immune-priming Lead-in, administration may be held for up to 1 week to allow for recovery.

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 9.

Table 9: 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.

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 6, Section 6.6.2, Section 6.6.3, and Section 6.6.4 for toxicities requiring permanent discontinuation of nivolumab, INO-5151, and/or CDX-301.

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 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 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 11 will be sent to the study site's local laboratory for analysis:

Table 11: 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, Inovio Pharmaceuticals, Celldex Therapeutics, 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 pharmacokinetics (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 will be performed using a validated assay method under the supervision of the Sponsor's designee.

8.6 IMMUNOGENICITY AND ANTI-DRUG ANTIBODIES

Immunogenicity samples will be collected according to the SOA to enable evaluation of immune response against PSMA and/or PSA and anti-drug antibodies (ADA) to 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.

The detection and characterization of immune response against PSA and/or PSMA may be performed using enzyme-linked immunospot (ELISpot) assays or other assays.

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. Additionally, immune response against PSMA and PSA maybe be evaluated by ELISpot.

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 AEs described in Table 6, as demonstrated in Table 12.

Table 12: 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 13 shows the width of 95% confidence intervals calculated for possible observed rates of AEs described in Table 6 within the study.

Table 13: Incidence with 95% Confidence Intervals of Possible Observed Adverse Events Described in Table 6

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 6

[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 C-1: MANAGEMENT ALGORITHMS

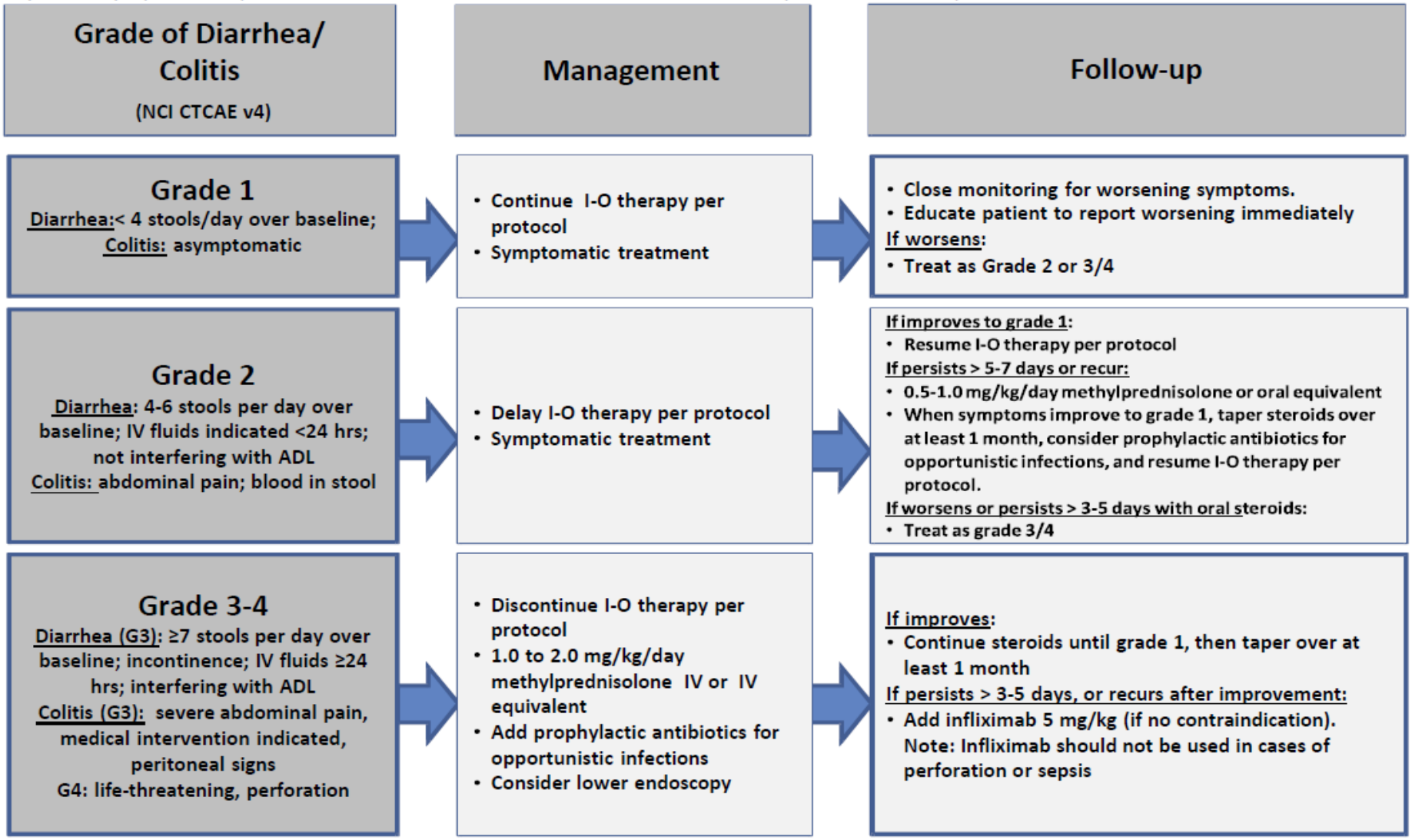
Management algorithms have been developed to provide guidance for Investigators in assessing and managing immune-mediated events in participants receiving nivolumab. Section 6.6.2 describes the criteria for dose delay and discontinuation to be followed for nivolumab in this cohort. These algorithms are intended to provide clinical recommendations. In cases in which the modification criteria in Section 6.6.2 and the algorithms differ, the criteria in Section 6.6.2 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

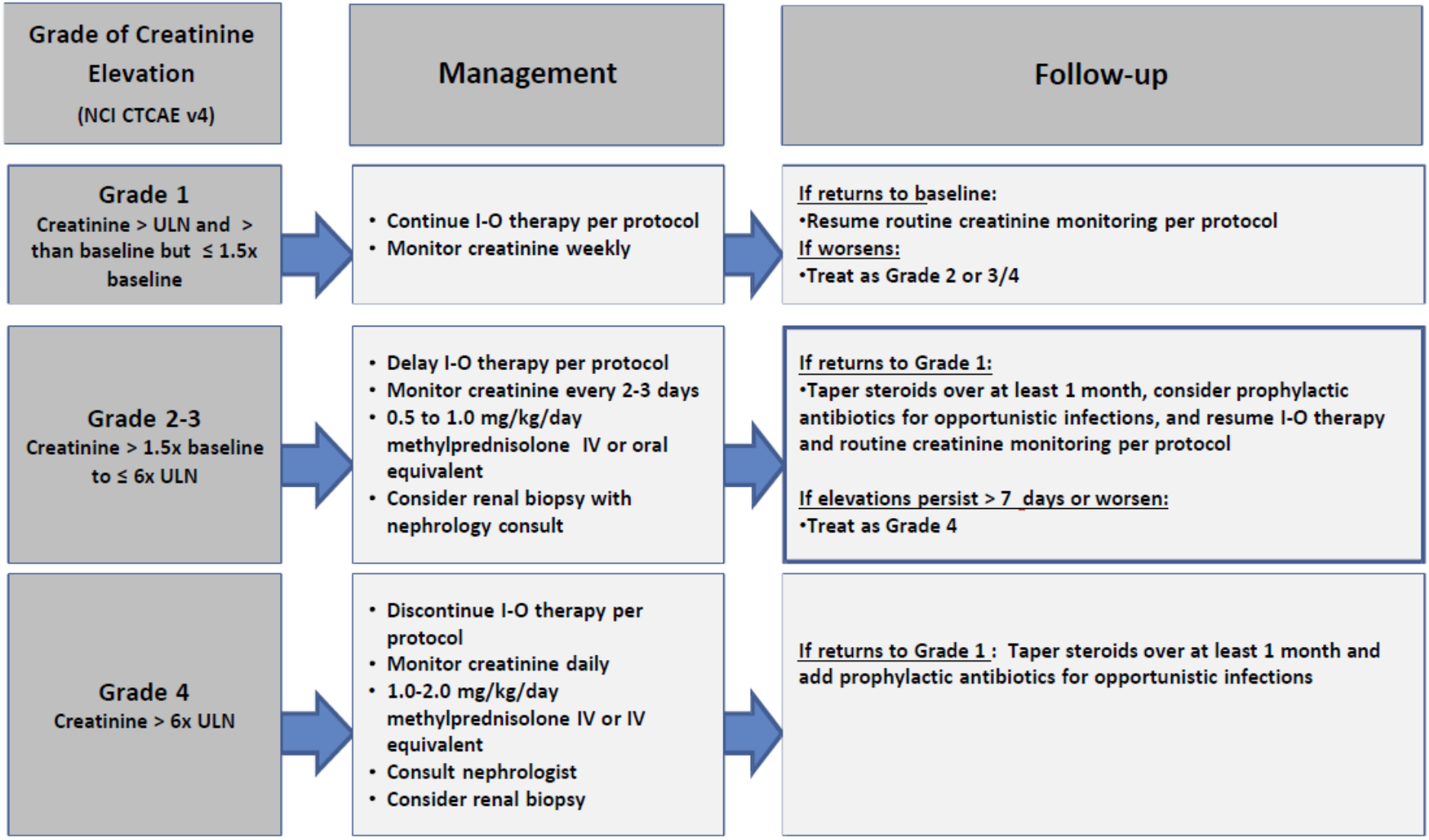
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

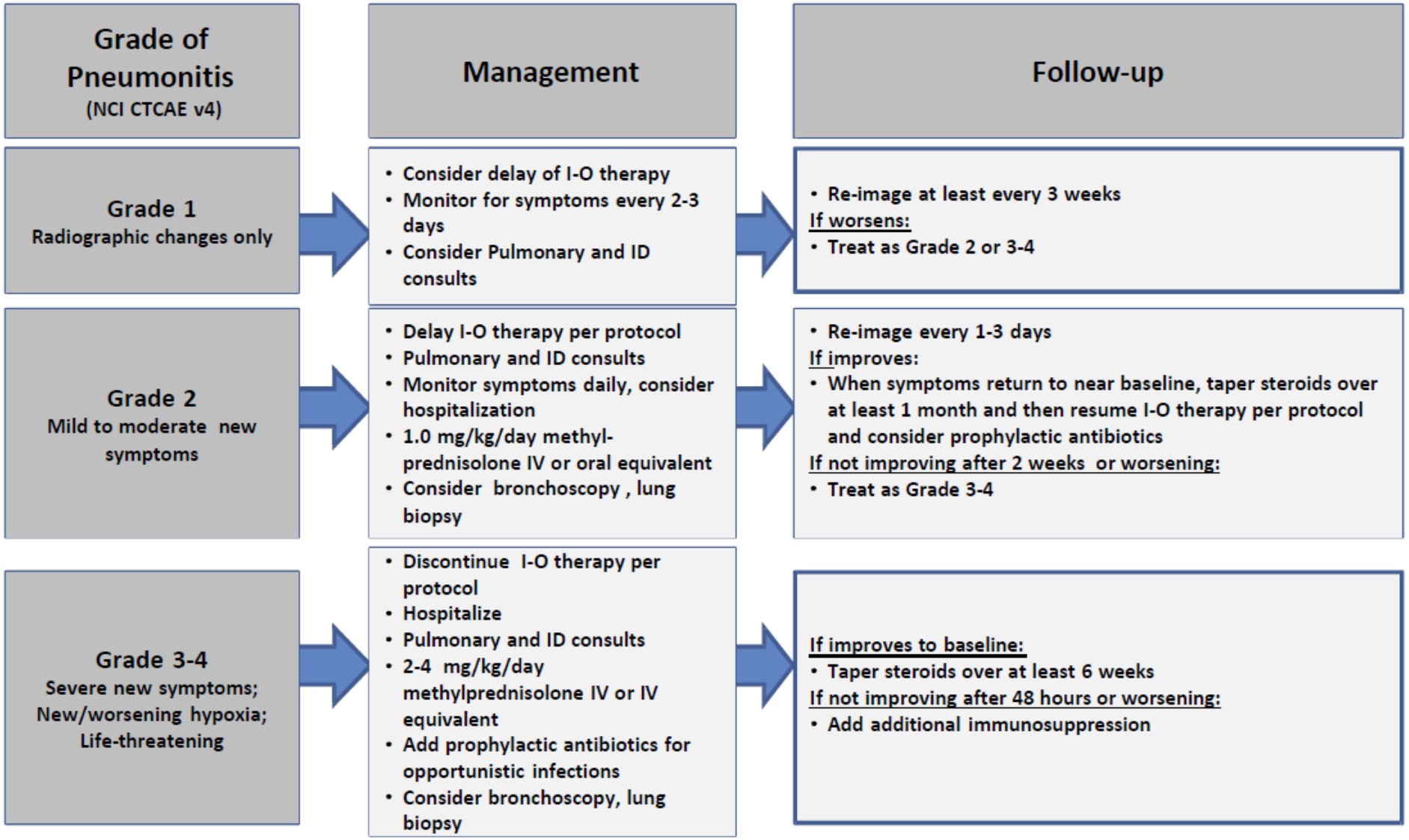
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

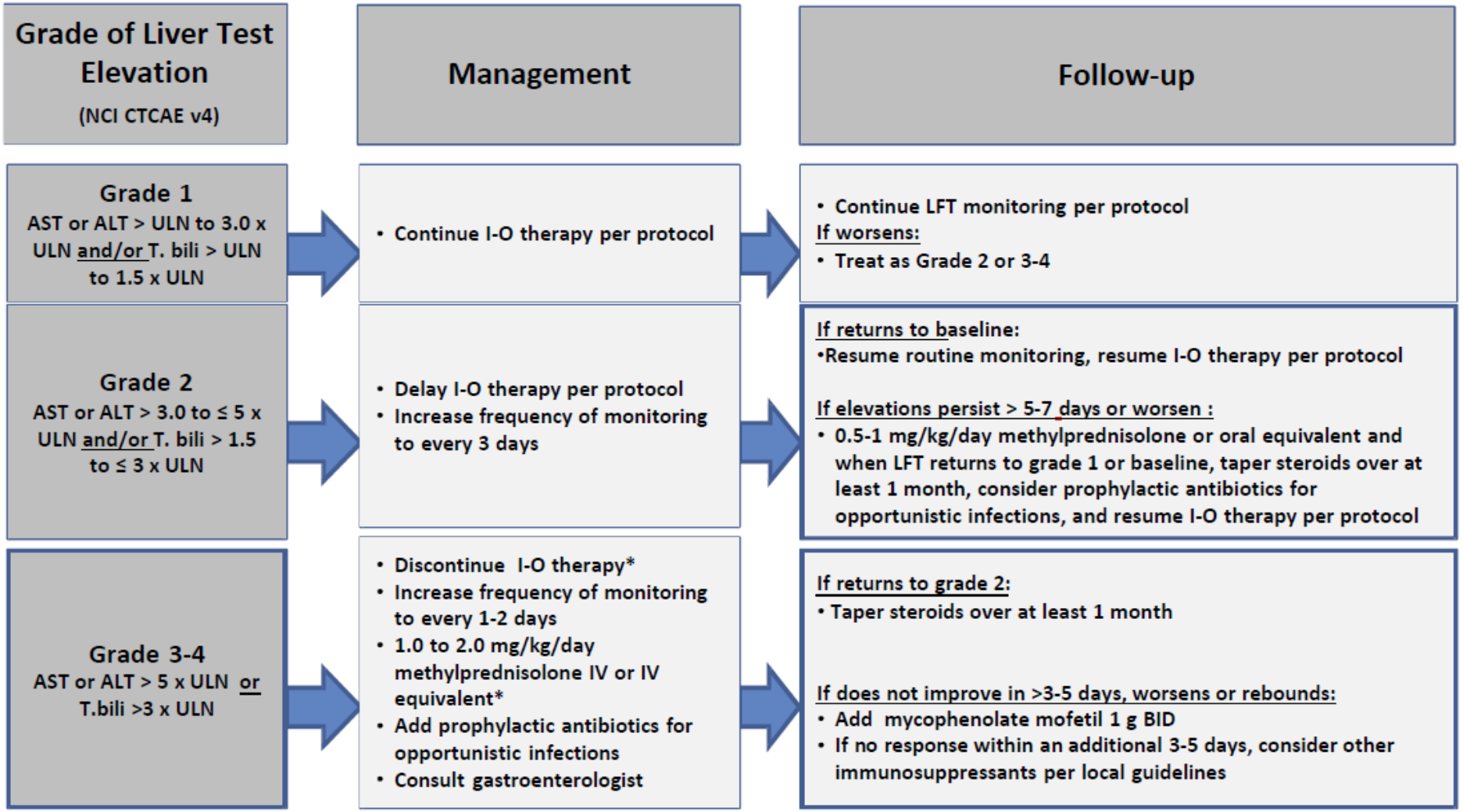
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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.

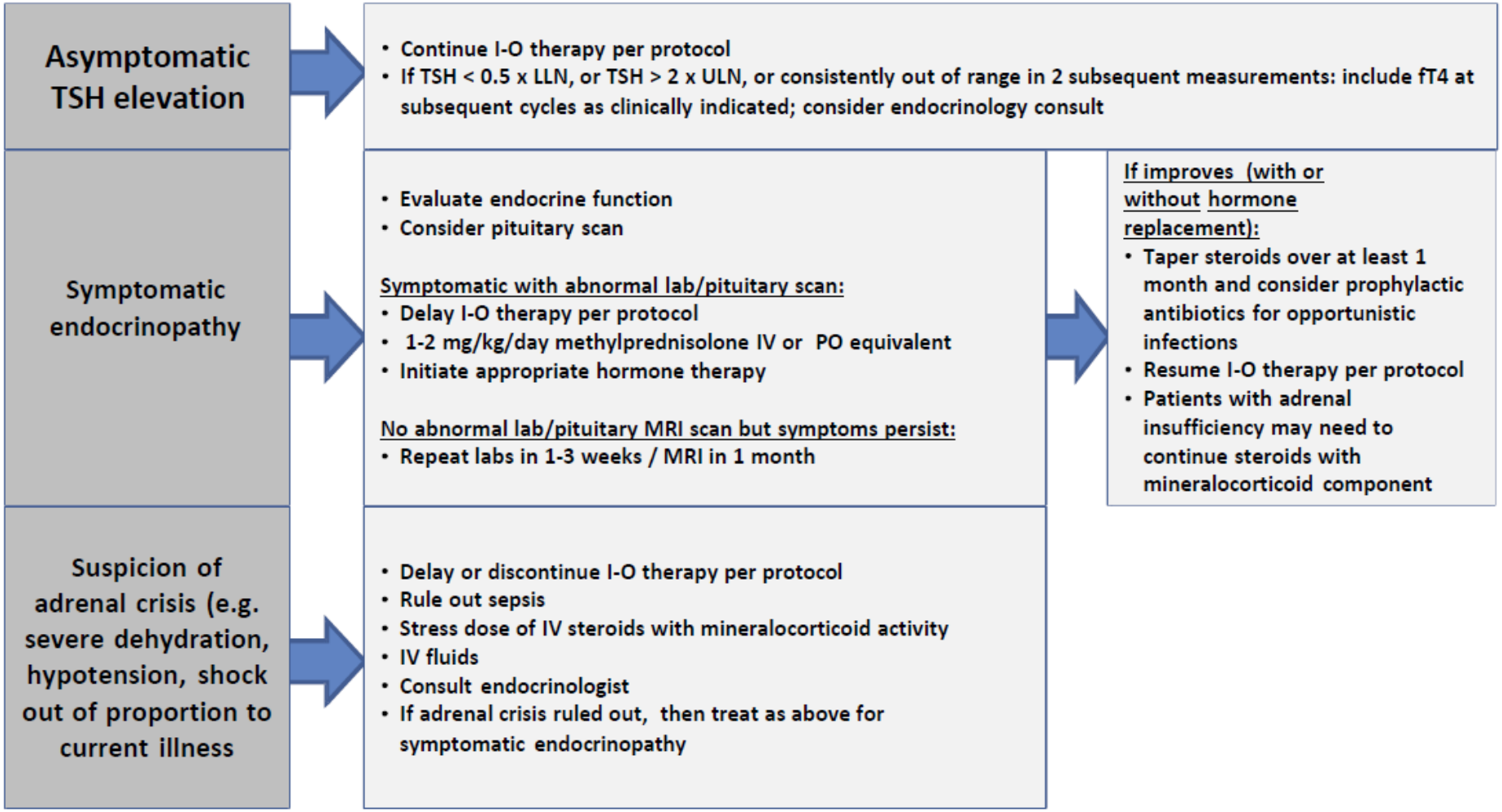


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

Endocrinopathy Adverse Event Management Algorithm

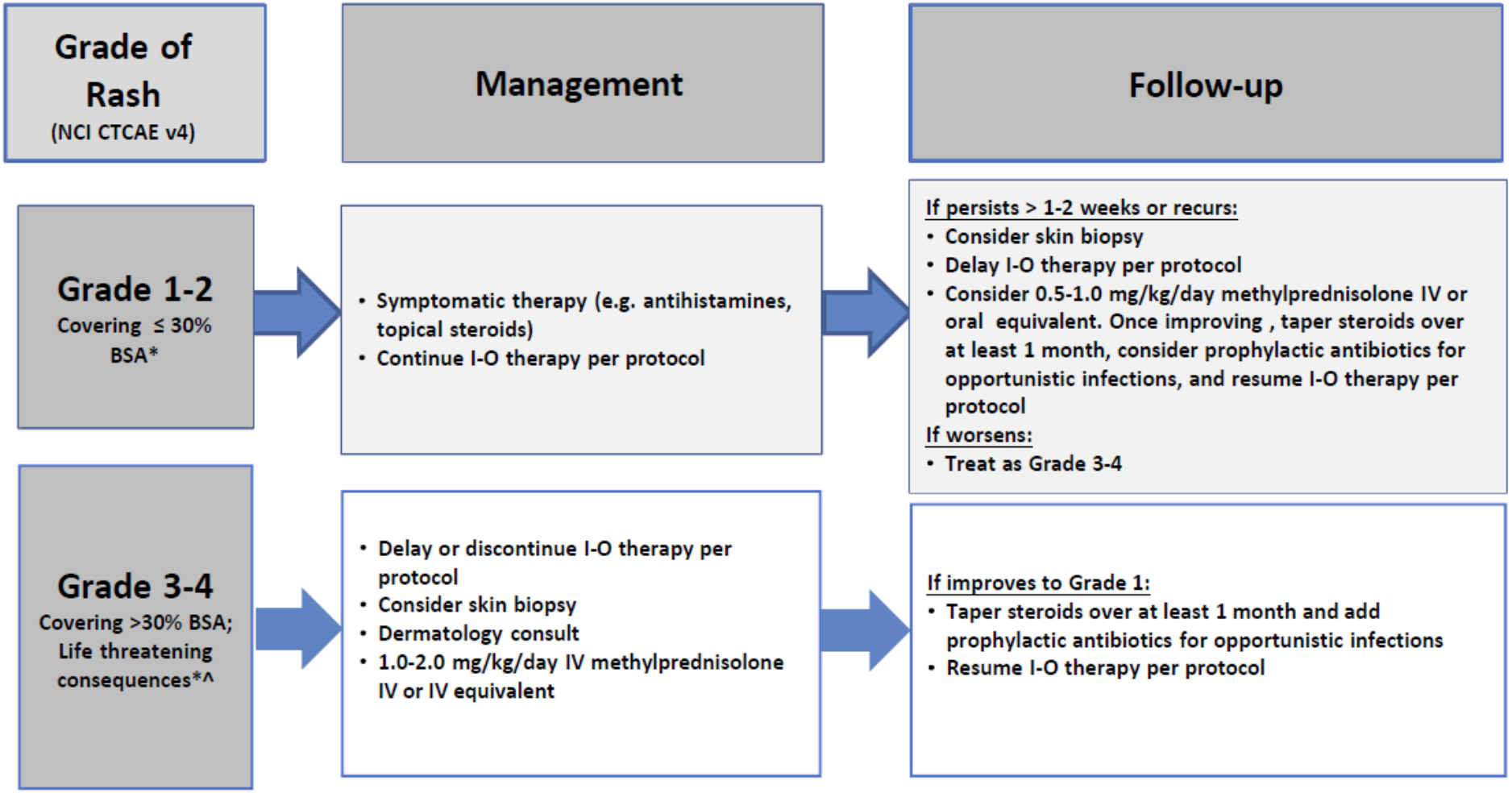
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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.



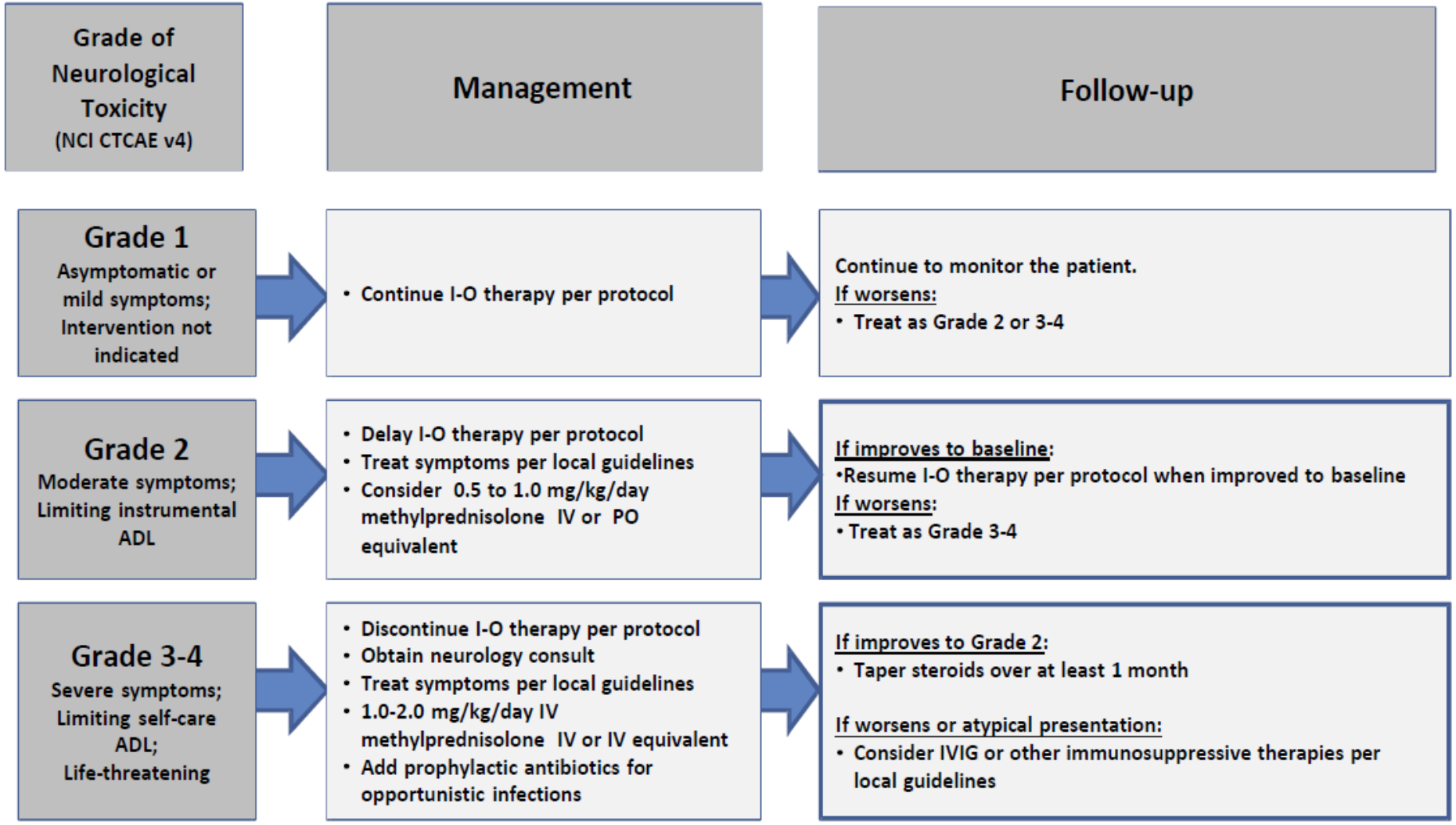
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of 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 C-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 C).
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)
ADC	antibody drug conjugates
ADP	adenosine diphosphate
AE(s)	adverse event(s)
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AML	acute myeloid leukemia
APC	antigen-presenting cells
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
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
CRPC	castration-resistant prostate cancer
CTCAE	Common Terminology Criteria for Adverse Events
CTL	cytotoxic T-lymphocyte
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
D	day
DC(s)	dendritic cell(s)
DCR	disease control rate
dMMR	mismatch repair deficient
DNA	deoxyribonucleic acid
DoR	duration of response
DT	doubling time
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISpot	enzyme-linked immunospot
EOT	end of treatment
EP	electroporation
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
HCC	hepatocellular carcinoma
HIV	human immunodeficiency virus
HPV	human papillomavirus
I/E	inclusion/exclusion
IB	Investigator's Brochure
ICF	informed consent form
IFN-γ	interferon gamma
IgG4	immunoglobulin G4
IM	intramuscular(ly)
IL-12	interleukin-12
INR	international normalized ratio
irAE(s)	immune-related AE(s)
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IV	intravenous(ly)

Abbreviation	Definition
LDH	lactate dehydrogenase
mAb	monoclonal antibody
mCRPC	metastatic castration-resistant prostate cancer
mRNA	messenger ribonucleic acid
MSI-H	microsatellite instability-high
NCI	National Cancer Institute
NK	natural killer
nmCRPC	nonmetastatic castration-resistant prostate cancer
NPCP	National Prostate Cancer Project
NSAIDs	nonsteroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PARP	poly ADP ribose polymerase
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programed cell death ligand 1
pDNA	plasmid DNA
PET	positron emission tomography
PFS	progression-free survival
PI	Principal Investigator
PK	pharmacokinetics
poly-ICLC	polyinosinic-polycytidylic acid stabilized with polylysine and carboxymethylcellulose
PORTER	Prostate Researching Translational Endpoints Correlated to Response
PPK	population pharmacokinetics
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q3M	every 3 months
Q3W	every 3 weeks
Q4W	every 4 weeks

Abbreviation	Definition
Q12W	every 12 weeks
QD	daily
RBC	red blood cell
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
rhIL-12	recombinant human IL-12
rhu	recombinant human
rhuFlt3L	recombinant human Flt3 ligand
RNA	ribonucleic acid
rPFS	radiographic progression-free survival
S	screening
SAC	Safety Assessment Committee
SAE(s)	serious adverse event(s)
SARS	severe acute respiratory syndrome
SC	subcutaneous(ly)
SCCHN	squamous cell carcinoma of the head and neck
SFU	spot forming units
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SIV	simian immunodeficiency virus
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
TNF-α	tumor necrosis factor alpha
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 C-3: APPENDIX COHORT C AMENDMENT HISTORY

DOCUMENT HISTORY	
Documents	**Date of Issue**
Amendment 1	30 Apr 2019
Original Appendix Cohort C	26 Feb 2019

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