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 A

Protocol Number: PICI0033

Amendment Number: Not applicable

Compound Number: NKTR-214, Nivolumab

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

Sponsor Name and Legal Registered Address:

Parker Institute for Cancer Immunotherapy
1 Letterman Drive
Suite D3500
San Francisco, CA 94129

Tel: 415-985-7311

Fax: 415-872-5305

Regulatory Agency Identifying Number(s):

IND NUMBER: 139269

EudraCT NUMBER: Not applicable

Approval Date: Final Protocol: 07 December 2018
Amendment 1: 24 January 2019

SPONSOR APPROVAL PAGE

Date: 25 JAN 2019

Ramy Ibrahim, MD
Chief Medical Officer

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

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

Signature: _____ Date: _____

Name (print): _____

Principal Investigator

Site Number: _____

Amendment(s) to Appendix Cohort A

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

Key Revisions in Amendment 1 (24 January 2019)

Section # and Name	Description of Change
Eligibility Criteria	
5.1 Inclusion Criteria	Combined previous inclusion criteria #6 and #10 into a single inclusion criterion #6.
Study Design	
1.3 Schema, Figure 1	Modified to improve identification of key research procedure time points.
Study Intervention	
6.6.1 Dose Modifications for the Combination of Nivolumab and NKTR-214	Added text related to written approval from the Medical Monitor to clarify that participants with toxicity that does not resolve or met retreatment criteria within 6 weeks of the last dose, must be discontinued from the combination therapy, unless written approval to restart therapy is provided by the Medical Monitor.
6.6.2 Dose Modifications Nivolumab	Added text related to written approval from the Medical Monitor to clarify that participants with toxicity that does not resolve or met retreatment criteria within 6 weeks of the last dose, must discontinue study intervention, unless written approval to restart therapy is provided by the Medical Monitor.
Clarification of Document	
General Revisions	Document updated to address minor typographical errors and editorial changes for clarity.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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 A

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 (ie, NKTR-214 and nivolumab) information that is not already available in the core protocol.

Rationale:

This study cohort is designed to explore the immune activation properties of NKTR-214 by induction of tumor infiltrating T and natural killer (NK) lymphocytes when used in combination with anti-programmed cell death 1 (PD-1) therapy in metastatic castration-resistant prostate cancer (mCRPC).

Objectives and Endpoints:

Refer to the core protocol.

Combination-specific exploratory objectives include:

Combination-specific Exploratory Objectives	Endpoints
• To evaluate the PK of NKTR-214 and/or nivolumab. • To evaluate the immunogenicity (ADA) of NKTR-214 and/or nivolumab.	• Sparse PK analysis • Presence of ADA against NKTR-214 and/or nivolumab.

ADA = anti-drug antibodies; PK = pharmacokinetics

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

Refer to the core protocol.

Intervention Groups and Duration:

Participants will be assigned to receive one of the enrolling immunotherapy combination study interventions. In this cohort, participants will receive NKTR-214 and nivolumab as follows:

Intervention	Dose	Frequency	Route	Schedule
NKTR-214	0.006 mg/kg	Q3W	IV over 30 (± 5) minutes	Starting Day 1
Nivolumab	360 mg	Q3W	IV over 30 minutes	Starting Day 1

IV = intravenous(ly); Q3W = every 3 weeks

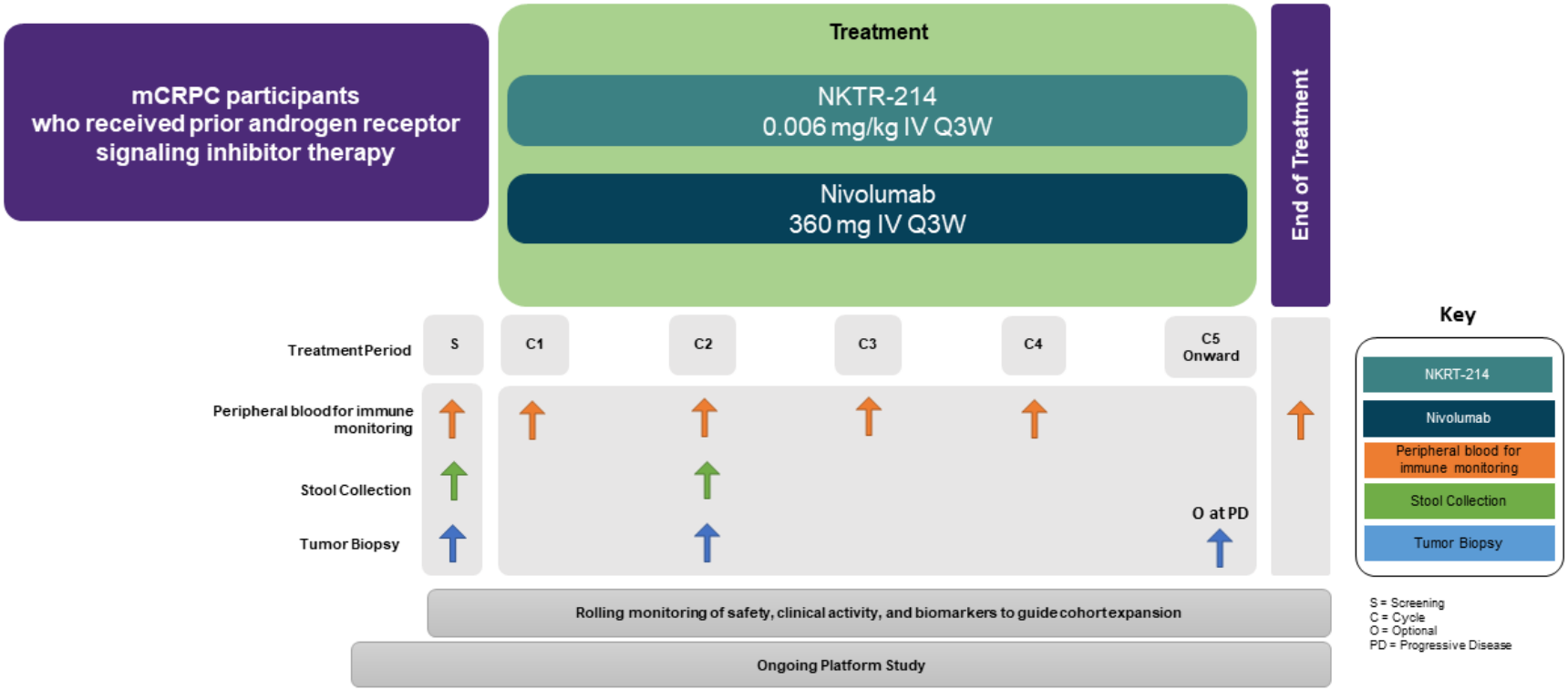
Participants will be administered intravenous (IV) fluid and provided guidelines for self-administered oral hydration following administration of NKTR-214.

NKTR-214 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 3 calendar weeks.

1.2 SCHEMA

The study schema is depicted in Figure 1.

Figure 1: Study Schema



IV = intravenously; mCRPC = metastatic castration-resistant prostate cancer; Q3W = every 3 weeks; S = screening

NKTR-214 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 3 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: NKTR-214 + Nivolumab								End of Treatment[b]	Follow-up	
		Cycle 1 (Q3W)				Cycles 2, 3, and 4		Cycle 5 Onward				
Day	Day -28 to Day -1	Day 1	Day 2	Day 3	Day 8	Day 1	Day 8	Day 1	Day 8	14 – 28 days after last dose	110 days after last dose	Q3M[c]
Window (days)	-28		± 1	± 1	± 1	± 3	± 1	± 3	± 3	± 7	± 10	± 14
Informed consent[d]	X											
Review of I/E criteria	X											
Medical/cancer history	X											
Physical examination	X	X				X		X		X		
ECOG performance status	X	X				X		X		X	X	
Vital signs (see Core Protocol Section 8.2.3)	X	X				X		X		X		
Body weight	X	X				X		X		X		
Hematology (see Table 11)	X	X[e]	X	X	X	X[e]	X	X[e]	X	X	X	
Clinical chemistry (see Table 11)	X	X[e]			X	X[e]	X	X[e]	X	X	X	
Urinalysis	X	X				X		X		X		
Prostate-specific antigen	X	X				X		X		X	X	
Testosterone level	X											
12-lead ECG	X	X	X	X	X	X		X				
ECHO/MUGA	X									X	X	
Circulating tumor cells[f]		X[e]				X[e]		X[e]		X		
cfDNA (blood)[g]	X					X[e] (Cycles 2 and 4)				X		
Circulating soluble analytes/PK/ADA[h]	X	X[e]	X		X	X[e] (Cycles 2, 3, and 4)				X		

Tests & Procedures	Screening/ Enrollment[a]	On-Treatment: NKTR-214 + Nivolumab								End of Treatment[b]	Follow-up	
		Cycle 1 (Q3W)				Cycles 2, 3, and 4		Cycle 5 Onward				
Day	Day -28 to Day -1	Day 1	Day 2	Day 3	Day 8	Day 1	Day 8	Day 1	Day 8	14 – 28 days after last dose	110 days after last dose	Q3M[c]
Window (days)	-28		± 1	± 1	± 1	± 3	± 1	± 3	± 3	± 7	± 10	± 14
NKTR-214 PK[i]	X	X[e]	X		X	X[e] (Cycles 2, 3, and 4)				X		
Blood immune biomarkers[h]	X	X[e]			X	X[e] (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]											
NKTR-214 administration[m]		X				X		X				
Administer IV fluids[n]		X				X		X				
Nivolumab administration[o]		X				X		X				
Radiographic disease assessment	X	At Week 9 (± 1 week), repeat every 9 weeks (± 1 week) for the first 27 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; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; I/E = inclusion/exclusion; IV = intravenously; MUGA = multigated acquisition; PD = progressive disease; PK = pharmacokinetics; Q3M = every 3 months; Q3W = every 3 weeks; SAE(s) = serious adverse event(s)

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

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

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

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

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

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

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

[h] Circulating soluble analytes, PK (nivolumab) 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), Day 2 of Cycle 1 (circulating soluble analytes), Day 8 of Cycle 1 (circulating soluble analytes, and blood immune biomarkers), prior to study intervention administration on Day 1 of Cycles 2-4, and at EOT.

[i] Pre-infusion blood samples will be collected to allow for PK evaluation of NKTR-214. PK blood samples will also be collected immediately post-infusion of NKTR-214 (prior to nivolumab administration) on Day 1 of Cycles 1-4. Additionally, PK blood samples will be collected on Day 2 and Day 8 of Cycle 1.

[j] Participants will undergo 2-3 tumor biopsies: prior to beginning study intervention (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] NKTR-214 will be administered at a dose of 0.006 mg/kg IV over 30 minutes Q3W on the same day as nivolumab 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 3 calendar weeks.

[n] At least 1 liter of IV fluid will be administered prior to NKTR-214 administration on the day of each NKTR-214 dose. For the next 3 days after administration (ie, Days 2-4 of each cycle), participants are required to drink at least 2 liters per day of self-administered oral hydration (note: alcohol and caffeine intake should not be counted toward the daily hydration requirements). Advise participants to restrain from strenuous activity and avoid long hot showers and saunas for Days 1 to 5 of each cycle. Per clinical discretion, IV fluids may be administered at any time. The Investigator may decide to forego administering IV fluids to a participant if this is deemed in the best interest of the participant (eg, evidence of fluid overload). Advise participants with orthostatic symptoms to call their treating oncologist and consider increasing oral hydration (see Section 6.1.1).

[o] Nivolumab will be administered at a dose of 360 mg IV over 30 minutes Q3W 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 3 calendar weeks. The time between nivolumab doses should not be less than 18 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

Immunotherapy has changed the landscape of treatments for a number of malignancies, resulting in marked clinical benefit for patients with cancers including metastatic melanoma, non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC). Studies of immunotherapy in patients with advanced prostate cancer have failed to yield similar results. A phase 3 randomized, controlled trial of ipilimumab after docetaxel in patients with metastatic castration-resistant prostate cancer (mCRPC) failed to meet its primary endpoint of overall survival (OS; Kwon et al., 2014), and early phase studies of programmed cell death 1 (PD-1) blockade in advanced malignancies did not demonstrate clinical activity in advanced prostate cancer (Topalian et al., 2012). However, emerging data suggest subsets of patients with prostate cancer, such as those with microsatellite instable tumors, which are enriched for neoantigens for T cells to respond to, may respond to anti-PD-1 immunotherapy (Graff et al., 2016).

The prostate has historically been thought to be an immune-privileged site, with disease evidence of intratumoral natural killer (NK) cells, macrophages, and 'low levels' of both CD4+ and CD8+ T cells in prostate tumor tissue (Flammiger et al., 2012; Sfanos et al, 2009; De Marzo et al., 2007; Massari et al., 2016). As a 'cold' tumor, the immunosuppressive microenvironment may contribute to the lack of clinical benefit to immunotherapy in prostate cancer, including low programmed cell death ligand 1 (PD-L1) expression (Martin et al., 2015), low mutational burden (Alexandrov et al., 2013), low abundance of intratumoral T cells (Flammiger et al., 2012), low cytolytic activity of NK cells (Pasero et al., 2016), and accumulation of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) in tumor bed (Miller et al., 2006; Lopez-Bujanda and Drake, 2017). Treatment-based approaches that address these mechanisms of immune evasion or identify immune-responsive patient subsets may allow for more successful immunotherapy treatment approaches for this patient population with high unmet medical need.

The T cell cytokine interleukin 2 (IL-2) is a potent antitumor cytokine, with a long clinical history as one of the first immunotherapeutic agents for the treatment of cancer. Aldesleukin (Proleukin®), which is approved by the United States (US) Food and Drug Administration (FDA) for metastatic melanoma and metastatic renal cell carcinoma, directly stimulates the immune system and has been shown to lead to durable responses in ~10% of people with metastatic melanoma and renal cancer (Payne et al., 2014). However, in addition to acting as a

stimulator of the immune system by activating tumor killing CD8+ T cells, aldesleukin also suppresses the immune system by activating Tregs (Boyman and Sprent, 2012).

Despite favorable clinical outcomes associated with aldesleukin, it has several therapeutic limitations, including the need for inpatient hospital administration, 5 consecutive days of dosing, and the potential for serious toxicities, including capillary leak syndrome, hypotension, and pulmonary edema requiring medical management in the intensive care unit. Nevertheless, a continued role for IL-2 in cancer immunotherapy exists, as patients treated with high dose IL-2 have long lasting durable responses, including patients considered non-responders with stable disease (SD) (McDermott et al., 2015). These data underscore the relevance of cytokines and the need for improved cytokine therapies in the era of immune checkpoint inhibitors.

2.2.1 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 US for the treatment of several cancer types, including unresectable or metastatic melanoma (as monotherapy or in combination with ipilimumab) and as monotherapy in previously-treated metastatic NSCLC, advanced RCC, relapsed or refractory classical Hodgkin lymphoma (cHL), locally advanced or metastatic urothelial carcinoma (UC); recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN), microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC), and hepatocellular carcinoma (HCC). In phase 1 investigation, nivolumab did not demonstrate clinical activity in 17 participants with mCRPC. This is consistent with mCRPC having a low level of immune cell infiltrate and 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 Investigator's Brochure (IB; Nivolumab Investigator's Brochure, 2018) and approved US prescribing information (Opdivo [nivolumab] US Prescribing Information [USPI], 2018) for detailed background information on nivolumab.

2.2.2 Background on NKTR-214 (Nektar Therapeutics)

NKTR-214 is a novel cytokine with enhanced immune system activation. NKTR-214 consists of IL-2, which has the same amino acid sequence as aldesleukin (recombinant human IL-2 [rhIL-2]), conjugated at a defined region within the protein to releasable polyethylene glycol (PEG) chains. In contrast to high-dose aldesleukin, which requires patients to be hospitalized for administration, NKTR-214 was designed as an outpatient therapy. In addition, NKTR-214 was

designed to mitigate the serious toxicities associated with rapid systemic immune activation seen with administration of high-dose IL-2 (NKTR-214 Investigator's Brochure, 2018).

NKTR-214 is a prodrug of a conjugated cancer immunotherapy cytokine that exerts its biological activity by binding to the IL-2 receptor and subsequent activation of effector T cells. The PEG chains of NKTR-214 render the molecule inactive. Upon intravenous (IV) administration, the PEG chains slowly release via hydrolysis to generate the active cytokine species (2-PEG-IL-2 and 1-PEG-IL-2) that have a peak plasma concentration 26 to 30 hours after infusion. The slow generation of the 2-PEG-IL-2 and 1 PEG-IL-2 significantly mitigates the rapid-onset, systemic cytokine-related toxicities associated with high dose IL-2. Furthermore, the prodrug design of NKTR-214 with its antibody-like dosing, and the long half-life (13 to 19 hours) and sustained CD122 signaling of the active NKTR-214 moiety, obviate the need for 5-day courses of thrice daily infusions, or of daily subcutaneous injections.

The polymer conjugation of NKTR-214 promotes biased signaling through the IL-2 receptor beta gamma (IL-2Rβγ). This unique feature preferentially increases the proliferation, activation and effector function of tumor antigen-specific CD8+ T cells and NK cells within the tumor microenvironment without expanding unwanted intra-tumoral Tregs that are activated through the IL-2 receptor alpha beta gamma (IL-2Rαβγ) (Charych et al., 2016a; Charych et al., 2016b). Specifically, the location of the NKTR-214 PEG chains interferes with the IL-2 alpha subunit responsible for the undesirable effect of activating Tregs in the tumor while continuing to permit binding to the IL-2Rβγ (CD122) receptor.

NKTR-214 also correspondingly promotes expression of PD-1 on the surface of CD8+ T cells and induction of a Type II interferon gene signature in the tumor microenvironment, driving cell surface expression of PD-L1 on tumor cells (Diab et al., 2017a). The immunogenic properties of NKTR-214 with the induction of tumor infiltrating lymphocytes and upregulation of the PD-1/PD-L1 axis makes NKTR-214 a potentially promising combination therapy for use with checkpoint inhibitors that target and inhibit the PD-1/PD-L1 pathway.

Multiple phase 1/2 clinical trials are currently underway in which NKTR-214 is administered either as monotherapy or in combination with immune checkpoint inhibitors, such as nivolumab, once every 2 or 3 weeks for the treatment of solid tumors (Charych et al., 2017). NKTR-214 has been generally well-tolerated in the clinical studies to date, with promising evidence of clinical efficacy in cancer patients, indicating a favorable benefit-risk profile. While no objective responses were observed in the single-agent study of NKTR-214 (Study 15-214-01 [EXCEL]), 9 patients experienced tumor shrinkage between 1% and 30%, and 2 patients, after progressing on multiple prior therapies, had durable SD > 1 year. One patient with metastatic melanoma, who was previously treated with ipilimumab and a BRAF inhibitor, received 25 cycles of NKTR-214 and had durable SD for 18 months. A second patient with metastatic RCC, who had progressed

on high dose IL-2 and was refractory to single-agent OX40 and nivolumab, was treated with 19 cycles of NKTR-214 and had durable SD for 14 months. Given the biological properties of NKTR-214 and nivolumab these observations further supported the rationale for combining these two agents.

NKTR-214 has been safely administered in an out-patient setting supported by appropriate clinical monitoring. Hypotension is the most clinical significant adverse effect can be effectively mitigated by prevention and hydration guidelines. Hypotension due to capillary leak syndrome as has been observed with the use of IL-2 has not been observed in the hypotension associated with NKTR-214, which appears to be due to a vasodilatory effect of the cytokines released in response to NKTR-214. Other common adverse events (AEs) associated with NKTR-214 appear to be largely cytokine-driven, are generally mild or moderate in severity and self-limiting.

Refer to the IB (NKTR-214 Investigator's Brochure, 2018 and Addendum 1 to NKTR-214 Investigator's Brochure, 2018) for detailed background information on NKTR-214.

2.2.3 Rationale for NKRT-214 + Nivolumab Immunotherapy Combination

Given the safety profile, modest antitumor activity, and observed pharmacodynamic effects of NKTR-214 on increasing PD-L1 expression and induction of interferon gene signature and T and NK lymphocytes in the tumor, a major focus of the development of NKTR-214 treatment is in combination with PD-1 checkpoint inhibitors. In an ongoing phase 1/2 study of NKTR-214 and nivolumab in immuno-oncology naive patients with locally advanced or metastatic solid tumor malignancies (Study 16-214-02 [PIVOT-02 study]), a total of 38 patients with melanoma, NSCLC, RCC were enrolled in the phase 1b dose-escalation cohort. Among these patients, clinical activity was observed in both PD-L1 negative and positive patients (Table 2). The recommended phase 2 dose for the combination is 0.006 mg/kg NKTR-214 and 360 mg nivolumab administered on the same day every 3 weeks (Q3W).

Table 2: Overall Tumor Response by Cancer Type: PIVOT-02 Dose-escalation Phase

	Melanoma (1L) (N = 11)	RCC (1L) (N = 14)	NSCLC (2L) (N = 4)	NSCLC (1/2L) (N = 5)
Best Overall Response (RECIST)				
ORR (CR + PR)	7 (64%)	10 (71%)	3 (75%)	3 (60%)
DCR (CR + PR + SD)	10 (91%)	11 (79%)	3 (75%)	4 (80%)
ORR by PD-L1 Status				
PD-L1 (-)	3/5 (60%)	5/8 (63%)	3/4 (75%)	3/5 (60%)
PD-L1 (+)	4/6 (67%)	4/5 (80%)	0	0
PD-L1 Unknown	0	1/1	0	0

Source: Diab et al., 2018

1L = first-line; 2L = second-line; CR = complete response; DCR = disease control rate; NSCLC = non-small cell lung cancer; ORR = objective response rate; PD-L1 = programmed cell death ligand-1; PR = partial response; Q3W = every 3 weeks; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease

Data included for the following doses studied: NKTR-214 0.006 mg/kg Q3W + nivoloumab 240 mg QW; NKTR-214 0.003 mg/kg Q2W + nivolumab 240 mg Q2W; 0.006 mg/kg Q2W + nivolumab 240 mg Q2W; 0.006 mg/kg Q3W + nivolumab 360 mg Q3W

Data cut: 29 May 2018

In the expansion cohort, 283 patients with melanoma, NSCLC, RCC, UC, or triple-negative breast cancer (TNBC) have been treated at the recommended phase 2 dose, including 18 first-line (1L) patients from the dose-escalation cohort (7 melanoma and 11 RCC; Diab et al., 2018). Three of the phase 2 expansion cohorts have met the prespecified efficacy criteria as of the 29 May 2018 data cutoff, supporting the evaluation of NKTR-214 and nivolumab in registrational trials (Table 3). Enrollment is ongoing for additional tumor types in immuno-oncology naive and refractory settings.

Table 3: Overall Tumor Response by Cancer Type: PIVOT-02 Expansion at Recommended Phase 2 Dose

	Melanoma Stage IV Naive 1L (N = 28)	RCC Stage IV Naive 1L (N = 26)	UC Stage IV Naive 1L (Cisplatin-ineligible) (N = 10)
Best Overall Response (RECIST)			
ORR (CR + PR)	14 (50%)	12 (46%)	6 (60%)
DCR (CR + PR + SD)	20 (71%)	20 (77%)	7 (70%)
ORR by PD-L1 Status			
PD-L1 (-)	5/12 (42%)	9/17 (53%)	3/5 (60%)
PD-L1 (+)	8/13 (62%)	2/7 (29%)	3/5 (60%)
PD-L1 Unknown	1/3 (33%)	1/5 (50%)	0

Source: Diab et al., 2018

CR = complete response; DCR = disease control rate; 1L = first-line; ORR = objective response rate; PD-L1 = programmed cell death ligand-1; PR = partial response; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; UC = urothelial carcinoma

Recommended phase 2 dose: NKTR-214 0.006 mg/kg in combination with nivolumab 360 mg every 3 weeks

Data cut: 29 May 2018

The combination is safe and well-tolerated at the recommended phase 2 dose, with a low rate of ≥ Grade 3 treatment-related AEs, including immune-mediated AEs (imAEs; Table 4). Cytokine-related toxicity is the most common toxicity observed in patients treated with NKTR-214 in combination with nivolumab. These toxicities, reported either as stand-alone clinical diagnoses or as the associated individual signs and symptoms, including flu-like symptoms, rash, pruritus, cytokine release syndrome, fatigue, and elevated hepatic transaminases, are generally mild or moderate in severity and are generally self-limiting.

Table 4: Safety: PIVOT-02 Expansion at Recommended Phase 2 Dose

Preferred Term	NKTR-214 0.006 mg/kg + Nivo 360 Q3W (N=283)
Treatment-Related AE Grade 1-2 in > 15%	
Flu-like symptoms[a]	166 (58.7%)
Rash[b]	126 (44.5%)
Fatigue	119 (42.0%)
Pruritus	89 (31.4%)
Nausea	62 (21.9%)
Decreased appetite	54 (19.1%)
Diarrhea	43 (15.2%)
Treatment-Related AE Grade 3 or higher (≥ 1% listed below)	**40 (14.1%)**
Hypotension	5 (1.8%)
Syncope	5 (1.8%)
Increased lipase	4 (1.4%)
Rash[b]	4 (1.4%)
Dehydration	3 (1.1%)
Patients who discontinued due to a TRAE	**6 (2.1%)**
Any Immune-Mediated AE (≥ Grade 3)	**10 (3.5%)**
≥ Grade 3 Immune-Mediated AE Treated with Steroid / Immunomodulating Medication	**7 (2.5%)**
Pneumonitis[c]/dyspnea	2 (0.7%)
Skin adverse event	2 (0.7%)
Hepatitis	1 (0.4%)
Colitis	1 (0.4%)
Elevated lipase	1 (0.4%)
≥ Grade 3 Endocrinopathy	**3 (1.1%)**
Diabetes mellitus treated with insulin	1 (0.4%)
Hyperglycemia treated with insulin	2 (0.7%)

Source: Diab et al., 2018

AE(s) = adverse event(s); MedDRA = Medical Dictionary for Regulatory Activities; Q3W = every 3 weeks; TRAE(s) = treatment-related adverse event(s)

Data cut: 07 May 2018

Patients are only counted once under each preferred term using highest grade

[a] Flu-like symptoms includes the following MedDRA preferred terms: chills; influenza; influenza-like illness; pyrexia.

[b] Rash includes the following MedDRA preferred terms: rash; rash erythematous; rash maculo-papular; rash pruritic; erythema; rash generalized; rash popular; rash pustular; rash macular

[c] One treatment-related Grade 5 pneumonitis related to nivolumab in a patient with NSCLC pretreated with carboplatin/pemetrexed and history of brain metastases

Translational data from the PIVOT-02 study confirm the rationale for activation of the immune system in the tumor microenvironment, with a conversion of PD-L1 negative tumors to PD-L1 positive on treatment in 9/17 (53%) of patients (Diab et al., 2018).

Given that NKTR-214 administration results in increasing PD-L1 expression and induction of interferon gene signature and T and NK lymphocytes in the tumor, it may overcome some of the immune evasion mechanisms identified in mCRPC. NKTR-214 is a potentially promising immune-activating agent in combination therapy with checkpoint inhibitors targeting the PD-1/PD-L1 pathway, such as nivolumab. Moreover, the side effect profile of NKTR-214 does not overlap with that of checkpoint inhibitors, further supporting the use of NKTR-214 as a potentially complimentary combination partner with nivolumab.

2.3 BENEFIT/RISK ASSESSMENT

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.

For monotherapy, the safety profile is similar across tumor types. Most 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).

NKTR-214

NKTR-214 has been generally well-tolerated in the clinical studies to date, both as monotherapy as well as in combination with immune checkpoint inhibitors, such as nivolumab, with promising evidence of clinical efficacy indicating a favorable benefit-risk profile (NKTR-214 Investigator's Brochure, 2018). NKTR-214 has been safely administered in an out-patient setting supported by appropriate clinical monitoring.

The most clinically important risk, hypotension, can be effectively mitigated by prevention and hydration guidelines. Other common AEs associated with NKTR-214 appear to be largely cytokine-driven, are generally mild or moderate in severity and self-limiting. Importantly, although cases of hypothyroidism, thyroiditis, and vitiligo/hypopigmentation consistent with immune-mediated mechanism have been observed in participants receiving NKTR-214 plus nivolumab, there is no evidence that NKTR-214 increases the frequency or severity of imAEs associated with immune checkpoint inhibitors. The risk mitigation strategy and measures described for this immunotherapy combination are considered robust and adequate to safe guard participants from clinically significant toxicities.

NKTR-214 and Nivolumab

The safety profile of nivolumab is well characterized and manageable when administered alone or in combination, including regimens where it is administered in combination with additional immuno-oncology products. The risk of hypotension with NKTR-214 seen in the monotherapy study was mitigated by the implementation of a hydration protocol in the PIVOT-02 study and these guidelines will be used in the current study. The current aggregate safety data for patients treated with the combination appears similar to nivolumab monotherapy. Nonclinical data, as well as clinical experience with high dose IL-2 and checkpoint inhibitor combinations, indicate the potential for improvement in therapeutic response compared with either agent given alone. 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 5.

Table 5: Cohort-Specific Objectives and Corresponding Endpoints

Objectives	Endpoints
Primary	
• To determine the safety of NKTR-214 + nivolumab in participants with mCRPC.	Refer to the core protocol.
Secondary	
• To determine the ORR of NKTR-214 + nivolumab in participants with measurable mCRPC. • To determine the DCR ≥ 9 months of NKTR-214 + nivolumab in participants with measurable mCRPC. • To evaluate the rPFS of NKTR-214 + nivolumab in participants with mCRPC. • To estimate the OS of NKTR-214 + nivolumab in participants with mCRPC.	Refer to the core protocol.
Exploratory	
• To evaluate the PK of NKTR-214 and/or nivolumab. • To evaluate the immunogenicity (ADA) of NKTR-214 and/or nivolumab. Refer to the core protocol for overall exploratory objective(s).	• Sparse PK analysis. • Presence of ADA against NKTR-214 and/or nivolumab. Refer to the core protocol for overall exploratory endpoint(s).

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

4 STUDY DESIGN

4.1 OVERALL DESIGN

In this study intervention cohort, NKTR-214 and nivolumab will be administered Q3W 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.

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

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The scientific rationale for this combination is provided in Section 2.2.3.

4.3 JUSTIFICATION FOR DOSE

The doses of NKTR-214 and nivolumab proposed for this study have been established as being safe, resulting in pharmacodynamic activity and having antitumor activity in previous and ongoing clinical trials (Section 4.3.2 and Section 4.3.1.1, respectively). Further, the proposed doses are those currently under study as the recommended phase 2 dose in Study 16-214-02, the ongoing phase 1/2 study in subjects with locally advanced or metastatic solid tumor malignancies (Study 16-214-02 [PIVOT-02 study]; Diab et al., 2017b; Diab et al., 2018).

Based on the safety profiles of the individual components, as well as the safety data from the use of the combination of NKTR-214 and nivolumab in other disease populations, there does not appear to be overlapping toxicities. Therefore, this combination at the doses proposed is considered warranted for the evaluation of safety and efficacy in this population.

4.3.1 Rationale for Nivolumab Dose and Schedule

In the US, single-agent nivolumab was approved in 2014 at a dose of 3 mg/kg every 2 weeks (Q2W). Subsequently, population pharmacokinetics (PPK) and exposure response analyses were performed to support use of flat dosing regimens (ie, nivolumab 240 mg Q2W, 360 mg Q3W, and 480 mg every 4 weeks [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). 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).

4.3.1.1 Nivolumab 360 mg Q3W Dosing Regimen

Although not approved in the US, available data support the use of 360 mg Q3W. Following nivolumab 360 mg Q3W, Cavgss are expected to be similar to those following nivolumab 3 mg/kg or 240 mg Q2W, while Cminss are predicted to be 6% lower and are not considered to be clinically relevant. Cmaxss are predicted to be approximately ~23% 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. This less frequent dosing regimen (ie, Q3W vs Q2W) is designed to afford greater convenience to the target patient population and allow combination of nivolumab with other agents (Nivolumab Investigator's Brochure, 2018).

4.3.2 Rationale for NKTR-214 Dose and Schedule

The clinical pharmacology profile of single-agent NKTR-214 was assessed in Study 15-214-01 (Study 15-214-01 [EXCEL]). NKTR-214 was administered as a 15-minute intravenous infusion at dose levels of 0.003, 0.006, 0.009, and 0.012 mg/kg every 2 weeks (Q2W) or Q3W. The maximum tolerated dose (MTD) of NKTR-214, based on pre-defined dose limiting toxicity (DLT) criteria, was 0.009 mg/kg administered Q3W. Blood samples were analyzed for NKTR-214 related cytokines (NKTR-214-RC), NKTR-214 active cytokines (NKTR-214-AC), unconjugated IL-2, and PEG to characterize the pharmacokinetics (PK) and metabolism of NKTR-214 (NKTR-214 Investigator's Brochure, 2018).

Maximal concentrations of NKTR-214-RC were achieved shortly after the end of the first infusion of NKTR-214 and declined monoexponentially thereafter, remaining detectable for 8 to 11 days postdose and resulting in mean half-life values between 13 and 19 hours across dose levels. NKTR-214-RC maximum plasma concentrations (Cmax) and area under the curve (AUC) increased linearly with dose.

NKTR-214-AC concentrations increased gradually after dosing, achieving a mean time to Cmax (Tmax) between 26 and 30 hours postdose. After reaching Cmax, NKTR-214-AC declined monoexponentially in parallel to the decline in NKTR-214-RC, and remained detectable for 8 days postdose, resulting in mean half-life values between 13 and 23 hours.

NKTR-214-RC and NKTR-214-AC exposure were similar across participants within a dose cohort and between cycles, without indication of accumulation with either the Q3W or Q2W

administration schedules, as expected based on the half-life. NKTR-214-AC and NKTR-214-RC exposure increased linearly with dose over the dose range studied.

Unconjugated IL-2 was only sporadically detected, and when detected, was present only at low concentrations (0.5 to 7.1 ng/mL, with the majority near the quantitation limit of 0.5 ng/mL) indicating that unconjugated IL-2 does not contribute to plasma NKTR-214 exposure. Analysis of PEG is ongoing.

The effect of nivolumab on NKTR-214 PK was assessed in Study 16-214-02 (PIVOT-02), based on NKTR-214-RC exposure. Pharmacokinetics of NKTR-214-RC in combination with nivolumab appear similar to those after NKTR-214 monotherapy, suggesting no drug-drug interaction between NKTR-214 and nivolumab (NKTR-214 Investigator's Brochure, 2018).

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 ≥ 9.0 g/dL or ≥ 5.6 mmol/L without transfusion or erythropoietin (EPO) dependency (within ≤ 7 days of assessment)

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

    c. Platelet count ≥ 100,000/mm^3

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

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

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

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

    g. Albumin ≥ 2.5 mg/dL.

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

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

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

5.1.2 Combination-specific Inclusion Criteria

1. A documented left ventricular ejection fraction (LVEF) > 45% using standard echocardiogram (ECHO) or multigated acquisition (MUGA) scan test within 60 days prior to Cycle 1 Day 1.
2. Oxygen saturation ≥ 92% on room air.

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. Participants must not have received prior IL-2 therapy.
2. Has had prior therapy with any anti-PD-1 or anti-PD-L1 antibody (prior therapy with an anti-cytotoxic T-lymphocyte-associated protein 4 [CTLA-4] antibody is permitted).
3. Prolonged Fridericia's corrected QT interval (QTcF) > 450 ms at screening.

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. Need for > 2 antihypertensive medications for management of hypertension (including diuretics).

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

Complete hydration guidelines are provided in Section 6.1.1. For all cycles, at least 2 liters per day of self-administered oral hydration on Days 2 to 5 are recommended.

5.3.2 Activity

As part of the protocol hydration guidelines, participants should be advised to restrain from strenuous activity and avoid long hot showers and saunas for Days 1 to 5 of every cycle.

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 6.

Table 6: Study Intervention

Study Intervention Name	Dosage Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Sourcing
NKTR-214	Sterile lyophilized powder to be reconstituted with sterile water for injection and diluted with commercially available dextrose 5% or normal saline	1.0 mg/mL of IL-2	0.006 mg/kg	IV infusion	Nektar Therapeutics
Nivolumab	Aqueous solution	10 mg/mL	360 mg	IV infusion	Bristol-Myers Squibb

IV = intravenous

NKTR-214 0.006 mg/kg will be administered as an IV infusion over approximately 30 minutes (± 5 minutes) (see Section 4.3.2), followed approximately 30 minutes later by nivolumab 360 mg, administered as an IV infusion over approximately 30 minutes (see Section 4.3.1.1). Study intervention will be administered Q3W 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 3 calendar weeks.

The NKTR-214 dose will be determined by the participant's weight in kilograms, which will be determined before the start of each 3-week cycle. If the participant's weight is within 10% of the participant's weight on Day 1 of Cycle 1, the study drug dose does not need to be recalculated, depending on institutional guidelines/preference.

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 Hydration Guidelines for NKTR-214

Important safety information and hydration instructions are to be provided to participants.

For those participants enrolled in this cohort, at least 1 liter of IV fluid on will be administered prior to NKTR-214 administration on the day of each NKTR-214 dose. For the next 3 days after administration (ie, Days 2 – 4 of each cycle), participants should be instructed that they are required to drink at least 2 liters per day of self-administered oral hydration (note: alcohol and caffeine intake should not be counted toward the daily hydration requirements). Participants should be advised to restrain from strenuous activity and avoid long hot showers and saunas for Day 1 to Day 5 of each cycle of NKTR-214 administration. Per clinical discretion, IV fluids may be administered at any time. The Investigator may decide to forego administering IV fluids to a participant if this is deemed to be in the best interest of the participant (eg, evidence of fluid overload).

Participants should be advised to call their treating oncologist if they experience orthostatic symptoms and consider increasing oral hydration.

To mitigate the event of hypotension, consideration should be given to withholding antihypertensive medications, including diuretics, as well as other drugs with hypotensive properties as described Section 6.5.2.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

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

NKTR-214 drug product should be stored in a secure, locked area with temperature at monitored -20 °C (± 5 °C), as specified on the drug label.

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.

In addition to the prohibited therapy described in the core protocol, based on clinical evidence, the Investigator may decide to withhold antihypertensive medications, including diuretics, as well as other drugs with hypotensive properties (eg, alpha blockers for benign prostatic hypertrophy) prior to each dose of NKTR-214, particularly when therapy involves multiple anti-hypertensive drugs and classes other than thiazide diuretics. If discontinuing antihypertensive medications, discontinue no less than 12 hours and no more than 48 hours prior to each dose of NKTR-214. Antihypertensive medications may be reinstituted in between doses of NKTR-214 if the diastolic pressure exceeds 90 mm Hg and/or the systolic pressure exceeds 160 mm Hg.

6.6 DOSE MODIFICATIONS

6.6.1 Dose Modifications for the Combination of Nivolumab and NKTR-214

Study participants may not have any dose escalation or dose reduction of nivolumab in this study; dose reduction, but not dose escalation, of NKTR-214 is allowed.

Participants who experience an AE described in Table 7 will be permanently 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 7 will continue throughout the study.

The Investigator may attribute each AE to the combination or any individual component of the study intervention. Holding of 1 agent and not the other agents is appropriate if, in the opinion of the Investigator, the toxicity is clearly related to 1 of the study interventions. If an Investigator believes a toxicity is uniquely related to one agent, then appropriate documentation is required regarding the drug to which the Investigator is attributing the AE. If, in the opinion of the Investigator, the toxicity is related to the combination of nivolumab and NKTR-214 then all 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 6 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 nivolumab and NKTR-214, as well as the measures to be taken, are outlined in the following sections. The combined effect of NKTR-214 and nivolumab on the AE or immune-related AE (irAE) profiles of these agents continues to evolve. Guidance with respect to the individual agents is provided in Section 6.6.2 and Section 6.6.3. Refer to the USPI for nivolumab (Opdivo USPI, 2018) and the Investigator's Brochures for nivolumab and NKTR-214 for complete summaries of safety information.

Table 7: Toxicity Criteria Requiring Permanent Treatment Discontinuation

Participants should be monitored for the occurrence of any of the following AEs that are considered by the Investigator to be possibly, probably, or definitely related to nivolumab, NKTR-214, 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 or that is clinically significant
• 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:
  ○ Endocrinopathy AEs, such as adrenal insufficiency, adrenocorticotropic hormone (ACTH) deficiency, hyper- or hypothyroidism, that resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose intolerance managed with glucose-controlling agents
  ○ Amylase or lipase elevations that last ≤ 7 days
  ○ Electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  ○ Tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor
  ○ Grade 3 nausea, vomiting, or diarrhea that can be medically managed to ≤ Grade 2 within 72 hours
  ○ Grade 3 hypotension during Cycles 1 or 2 that lasts ≤ 48 hours post-dose
  ○ Fatigue that improves to ≤ Grade 2 with 7 days
  ○ Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care
• 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

ACTH = adrenocorticotropic hormone; AE(s) = adverse event(s); ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

6.6.1.1 Potential for Overlapping Toxicities with Nivolumab and NKTR-214

Based on the safety profile observed with ongoing use of this combination, the toxicities associated with the monotherapy administration of nivolumab and NKTR-214 do not overlap 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 and Stevens-Johnson syndrome), 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.

Cytokine-related toxicity is the most common toxicity observed in patients treated with NKTR-214 monotherapy and NKTR-214 in combination with nivolumab. These toxicities, reported either as stand-alone clinical diagnoses or as the associated individual signs and symptoms, including flu-like symptoms, rash, pruritus, cytokine release syndrome, fatigue, and elevated hepatic transaminases are generally mild or moderate in severity, and are self-limiting.

Thyroid dysfunction, reported as hypothyroidism, thyroiditis (may be characterized by initial hyperthyroidism followed by hypothyroidism), or hyperthyroidism, occurred primarily in patients receiving combination therapy with NKTR-214 and nivolumab. Most of the cases were mild or moderate in severity, asymptomatic, and managed by hormone replacement therapy without corticosteroids.

Frequent and significant eosinophilia has been observed in patients receiving both single agent NKTR-214 and NKTR-214 plus nivolumab, primarily starting at Cycle 2 or later, consistent with a known effect of IL-2 therapy. The frequency of selected AEs (primarily Grade 1 or 2 in severity) such as rash, pruritus, edema, nausea, vomiting, diarrhea and dizziness increased with level of eosinophilia. Isolated cases of suspected hypereosinophilic syndrome have been reported. Absolute eosinophil count should be closely monitored per protocol.

6.6.1.2 Dose Modifications and Toxicity Management for Adverse Events Associated with Nivolumab and NKTR-214

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 A-1) have been developed to assist Investigators in assessing and managing the following 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-related Reactions Associated with the Administration of NKTR-214 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 should be reported within 24 hours to the study Medical Monitor and reported as a serious adverse event (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-related reactions are provided in Table 8.

Table 8: Dose Modification and Toxicity Management Guidelines for Infusion-related Reactions Associated with the administration of NKTR-214 and/or Nivolumab

Grade (NCI CTCAE v 5.0)	**Treatment**	**Premedication at Subsequent Dosing**
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	**Stop Infusion** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study intervention**	Participant may be premedicated according to local treatment guidelines
Grades 3 or 4 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 NKTR-214 + Nivolumab Combination Immunotherapy

Dose delays and interruptions are permitted for toxicity reasons (see Section 6.6.2 and Section 6.6.3).

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 6 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 (360 mg Q3W). 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 6 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 9.

AEs associated with nivolumab exposure may represent an immunologic etiology. These 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 9.

Table 9: 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]
	Serum creatinine more than 6 times the ULN	Permanently discontinue

Adverse Reaction	Severity[a]	Dose Modifications
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 NKTR-214

Dose delays and reductions are permitted for NKTR-214. Per recommendation of the Investigator and approval of the Sponsor's Medical Monitor, NKTR-214 dose may be delayed or reduced to 0.003 mg/kg based on observed drug-related toxicities. If the NKTR-214 dose is reduced to 0.003 mg/kg, the dose should remain at this level throughout the remainder of the study.

NKTR-214 may be delayed or reduced for the following reasons (considered to be related to NKTR-214):

- Grade 1 or 2 toxicity: No requirement for dose delay or dose reduction. If the toxicity persists at Grade 2 following completion of Cycle 1, a dose delay or dose reduction may be implemented at the discretion of the Investigator with the approval of the Medical Monitor.

- Grade 3 toxicity: NKTR-214 may be withheld if toxicity cannot be managed by adequate medical intervention. NKTR-214 dosing may resume at the same NKTR-214 dose or at a lower NKTR-214 dose level when toxicity resolves to Grade 1 or returns to baseline, except for instances where the potential recurrence of the event poses an undue risk for the participant.

If NKTR-214 is delayed, nivolumab administration can continue unless toxicity related to nivolumab would warrant a dose delay.

Participants will be permitted to resume study drug(s) at the same dose level(s) following resolution of an AE to ≤ Grade 1 or to baseline within 6 weeks after the last dose, with the exception of participants who meet criteria for permanent discontinuation as specified in Section 6.6.3.1. Participants who meet criteria for permanent discontinuation of NKTR-214 must permanently discontinue all study intervention.

If the decision is made to resume study drug(s) dosing, the participant should restart treatment on the next regularly scheduled study drug(s) dosing visit. Skipped doses are not to be replaced.

Participants may resume treatment when the drug-related AE(s) resolve(s) to ≤ Grade 1 or baseline, with the following exceptions:

- Participants may resume treatment in the presence of Grade 2 fatigue.
- Participants with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT or total bilirubin.
- Participants with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters (see Section 6.6.3.1) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible to resume study drug(s) treatment if discussed with and approved by the Medical Monitor.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the Medical Monitor.

Dose delay of NKTR-214 that results in treatment delay of > 6 weeks requires treatment discontinuation, with exceptions as noted in Section 6.6.3.1. However, if the toxicity resolves to ≤ Grade 1 or baseline > 6 weeks after the last dose, but the participant does not otherwise meet

the criteria for permanent discontinuation (see Section 6.6.3.1), and the Investigator believes that the participant is deriving clinical benefit, then the participant may be eligible to resume treatment with NKTR-214.

6.6.3.1 Permanent Treatment Discontinuation Criteria

Participants meeting any of the following criteria attributed to NKTR-214 will be required to permanently discontinue all treatment with NKTR-214. However, with Medical Monitor approval, NKTR-214 treatment may continue if the toxicities listed below are considered related to nivolumab only, provided the event does not meet criteria for delaying or discontinuation of nivolumab (see Section 6.6.2).

- Disease progression in the absence of clinical benefit (see details regarding continuing treatment beyond initial assessment of progression per PCWG3-modified RECIST 1.1 in Section 4.4 of the core protocol).
- Clinical deterioration, as assessed by the Investigator.
- Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 6 weeks or requires systemic treatment.
- Any ≥ Grade 2 drug-related pneumonitis or interstitial lung disease that does not resolve following dose delay and systemic steroids (also see Pulmonary Adverse Event Management Algorithm in Appendix A-1).
- Any Grade 3 nonskin, drug-related AE lasting > 7 days, with the following exceptions for uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, infusion reactions, endocrinopathies, and laboratory abnormalities:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
    - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation.
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
        - Grade 3 drug-related thrombocytopenia > 7 days associated with clinically significant bleeding requires discontinuation.

    - Any drug-related liver function test abnormality that meets the following criteria require discontinuation (also see Hepatic Adverse Event Management Algorithm in Appendix A-1):
        - AST or ALT > 5 × to 10 × ULN for > 2 weeks
        - AST or ALT > 10 × ULN
        - Total bilirubin > 5 × ULN
        - Concurrent AST or ALT > 3 × ULN and total bilirubin > 2 × ULN
- Any Grade 4 drug-related AE or laboratory abnormality, except for the following events, which do not require discontinuation:
    - Grade 4 neutropenia ≤ 7 days
    - Grade 4 lymphopenia or leukopenia ≤ 14 days in duration
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 or return to baseline within 7 days.
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
    - Grade 4 drug-related endocrinopathy AEs such as adrenal insufficiency, adrenocorticotropic hormone deficiency, hyper- or hypothyroidism, or glucose intolerance, that resolve or are adequately controlled with physiologic hormone replacement (corticosteroids at ≤ 10 mg of prednisone or equivalent per day, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Medical Monitor.
- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued treatment.
- Any dosing delay lasting > 6 weeks after the last dose, with the following exceptions:
    - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks after the last dose and with no more than 3 missed doses, the Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.

- Dosing delays > 6 weeks after the last dose that occur for nondrug-related reasons, may be allowed if approved by the Medical Monitor. Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks after the last dose and with no more than 3 missed doses, the Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed, and participants must otherwise meet the criteria for continued treatment at the time re-initiation of study intervention is considered.

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 7, Section 6.6.2, and Section 6.6.3 for toxicities requiring permanent discontinuation of nivolumab and/or NKTR-214.

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 doses must not be less than 18 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 for a description of the assessments for medical history and demographic data, physical examinations, vital signs, and electrocardiograms.

Descriptions of additional combination-specific assessments are provided in the following sections.

8.2.1 Increased Monitoring and Vital Sign Guidelines for Infusion-related Reaction or Hypotension

If the participant experiences a ≥ Grade 2 infusion-related reaction or hypotension during the days after NKTR-214 and/or nivolumab administration, the participant may be monitored overnight at the discretion of the Investigator. Longer periods of monitoring may be implemented at the discretion of the Investigator.

8.2.2 Echocardiograms

Standard ECHO will be performed to assess cardiac function and LVEF according to the SOA (Section 1.3). In the event of an abnormal ECHO, the Investigator may perform a stress ECHO (either exercise or nuclear). A MUGA scan can be performed to assess cardiac function and LVEF if a standard echocardiogram cannot be performed. The same assessment method should be used for the same participant throughout the study.

8.2.3 Clinical Safety Laboratory Assessments

8.2.3.1 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, Nektar 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 PK blood sampling will be collected according to the SOA to assess the PK of NKTR-214 and/or nivolumab.

PK profiles for NKTR-214 and/or nivolumab may be performed using a validated assay method under the supervision of the Sponsor's designee.

8.6 ANTI-DRUG ANTIBODIES

Immunogenicity samples will be collected according to the SOA to enable evaluation of anti-drug antibodies (ADA) to either NKTR-214 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 NKTR-214 and/or nivolumab may be performed using a validated assay method under the supervision of the Sponsor's designee.

8.7 BIOMARKERS

Refer to the core protocol.

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.

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 A-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

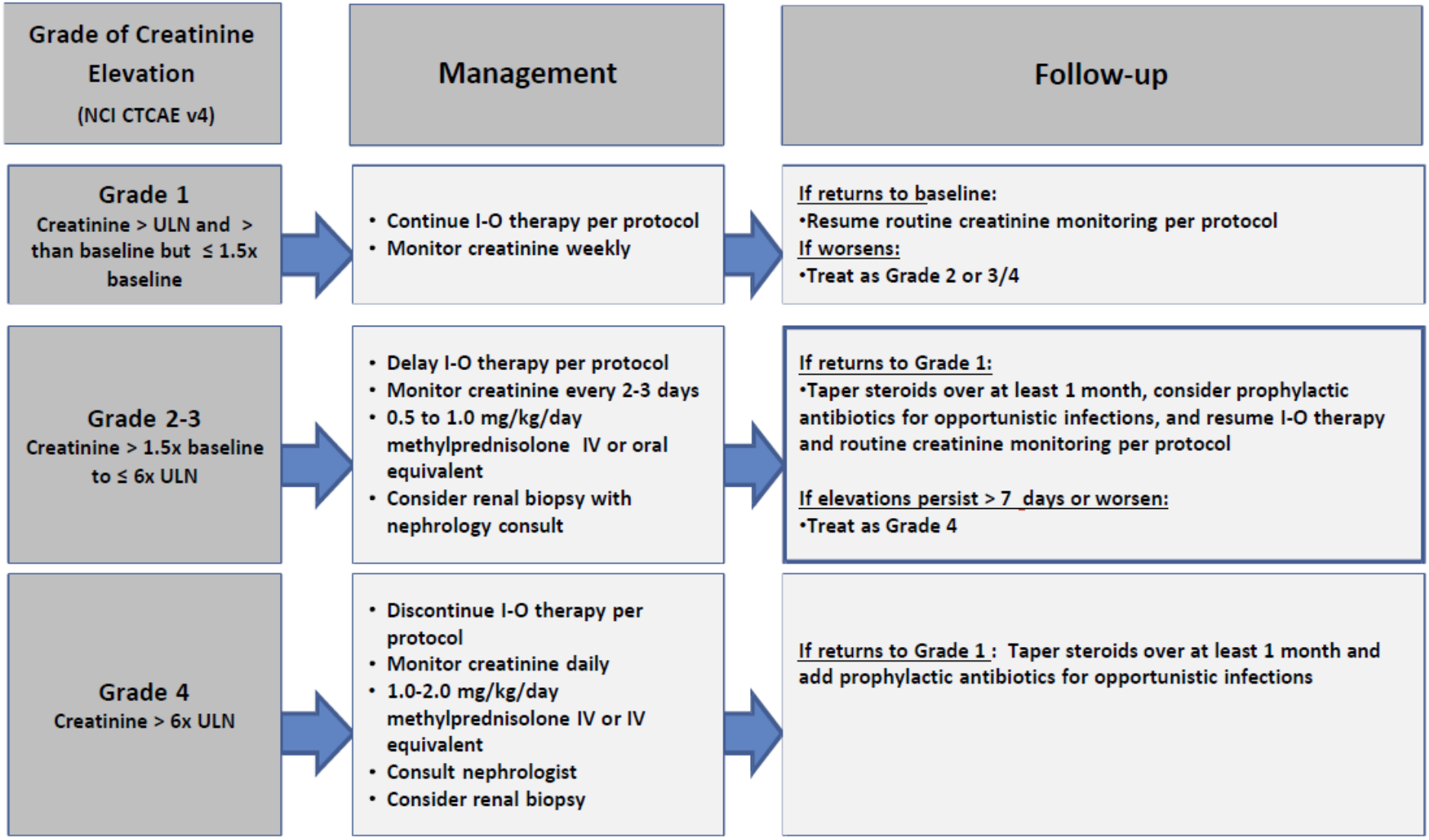
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: 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

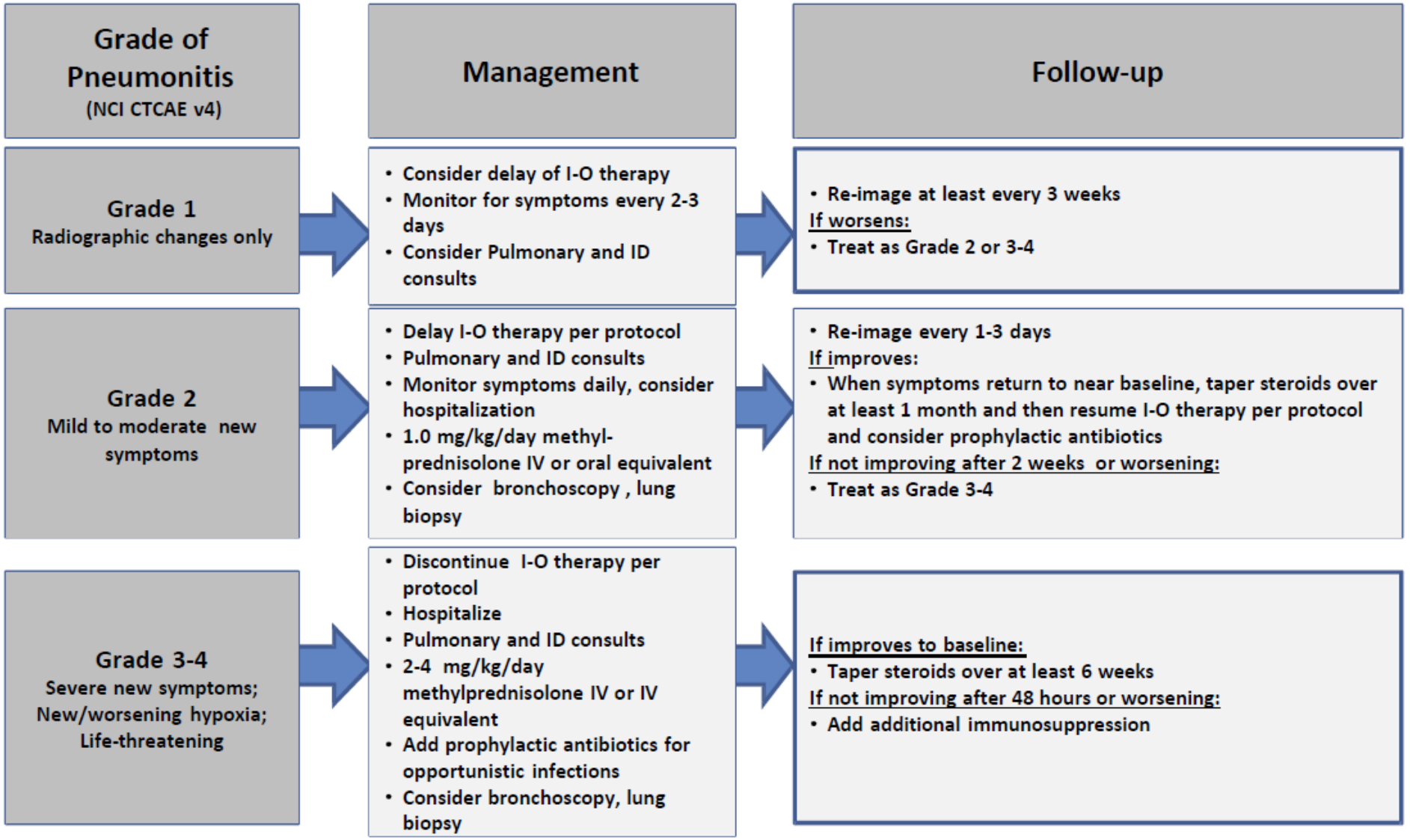
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

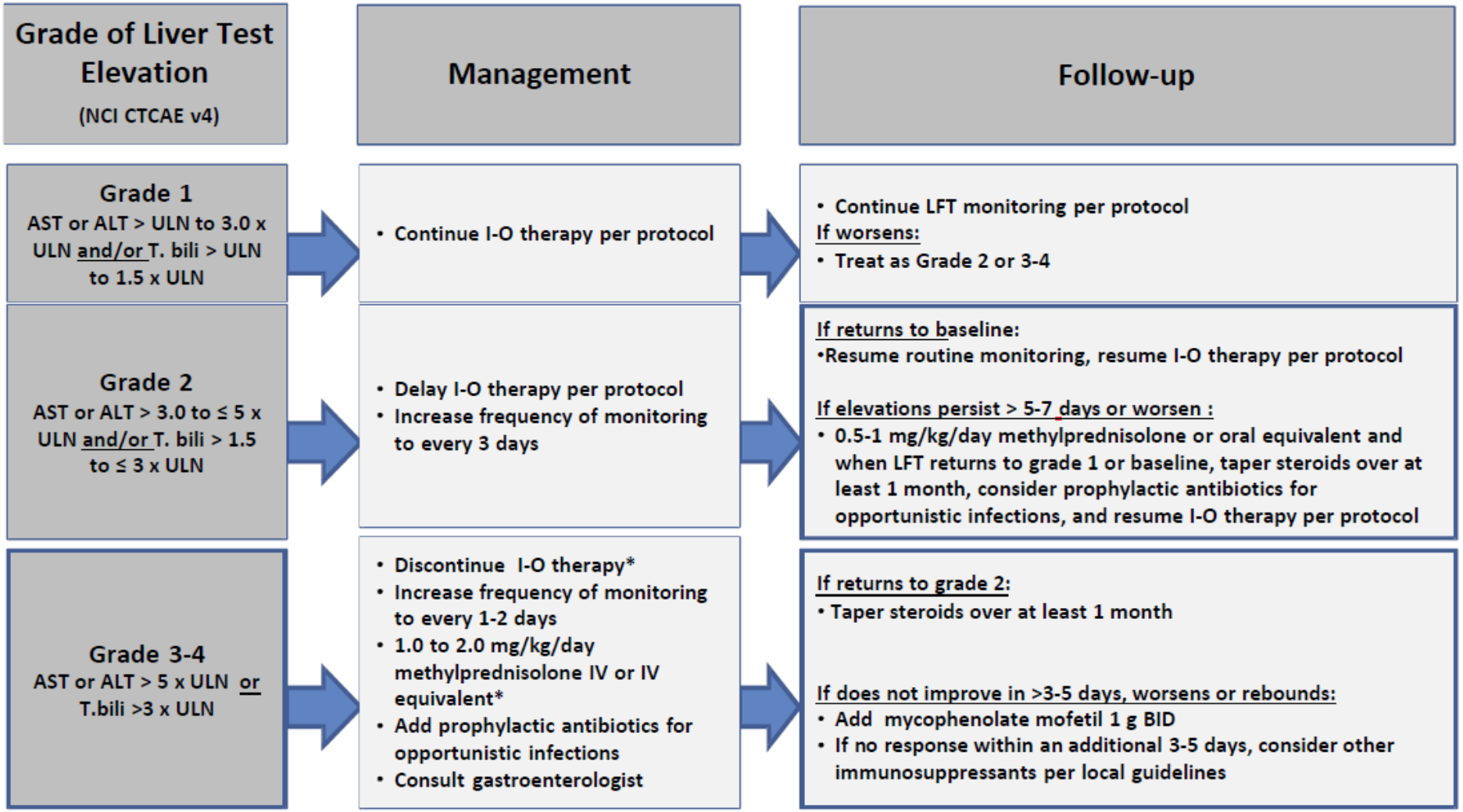
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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.

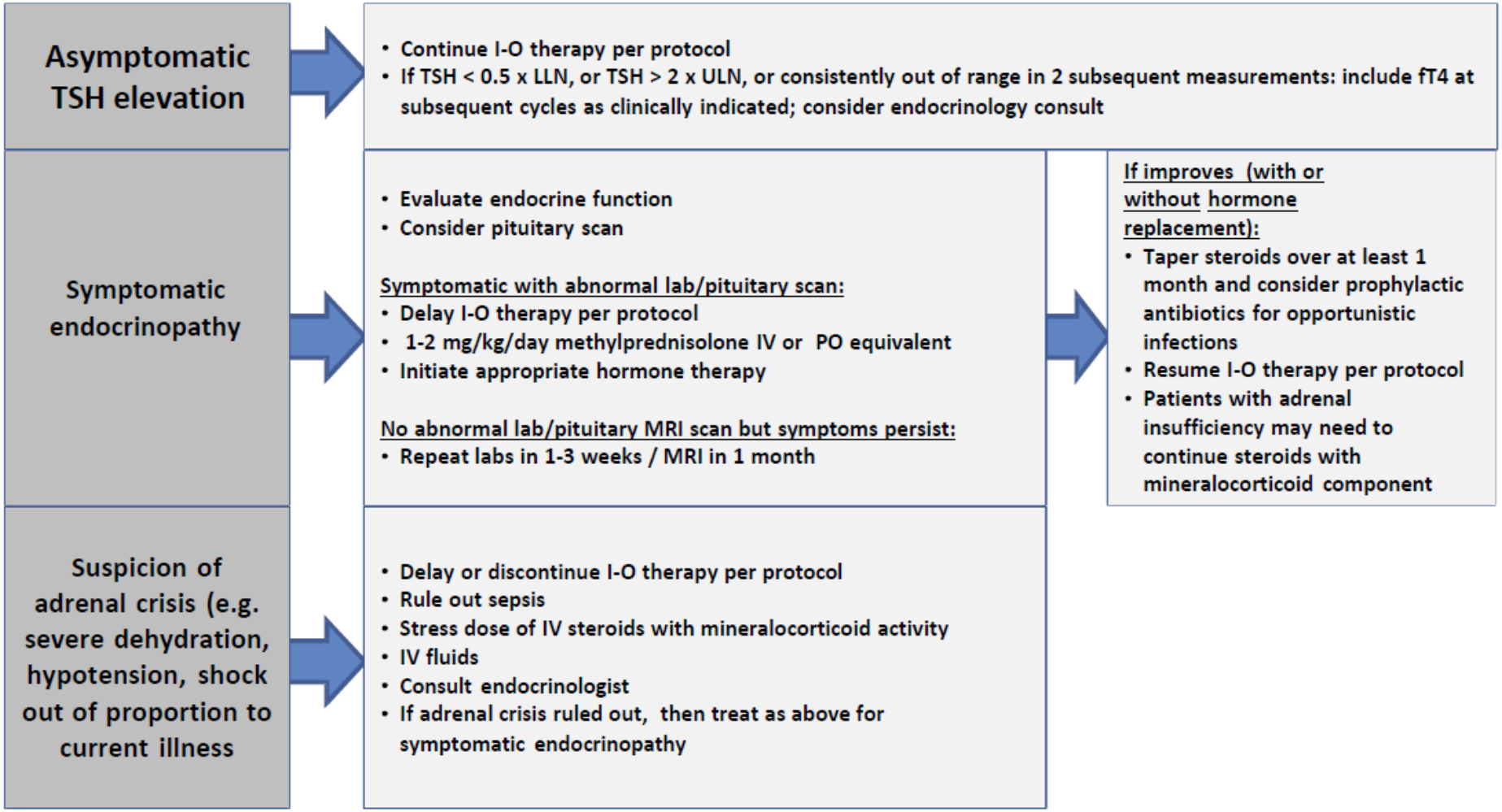


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

Endocrinopathy Adverse Event Management Algorithm

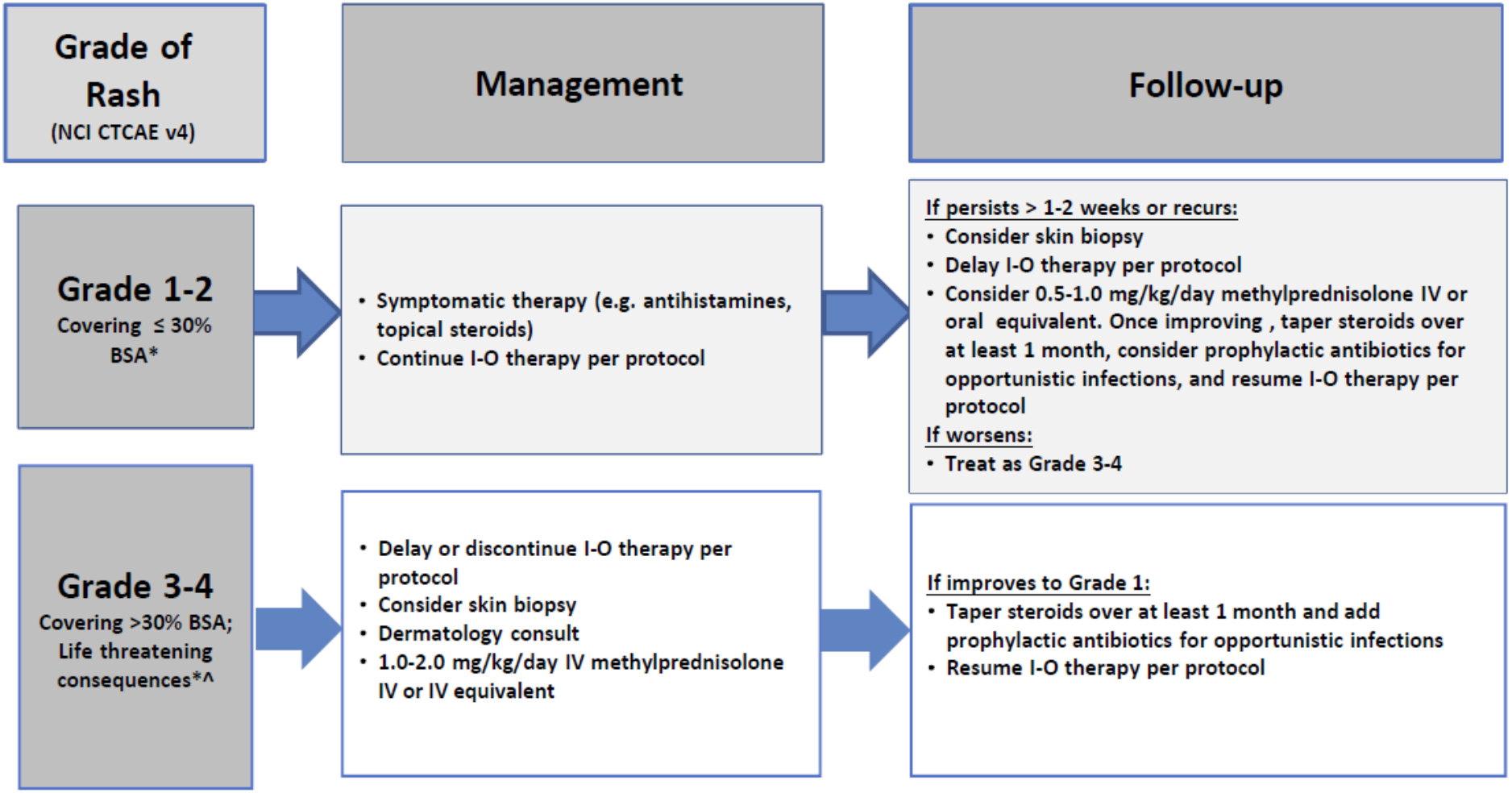
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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.



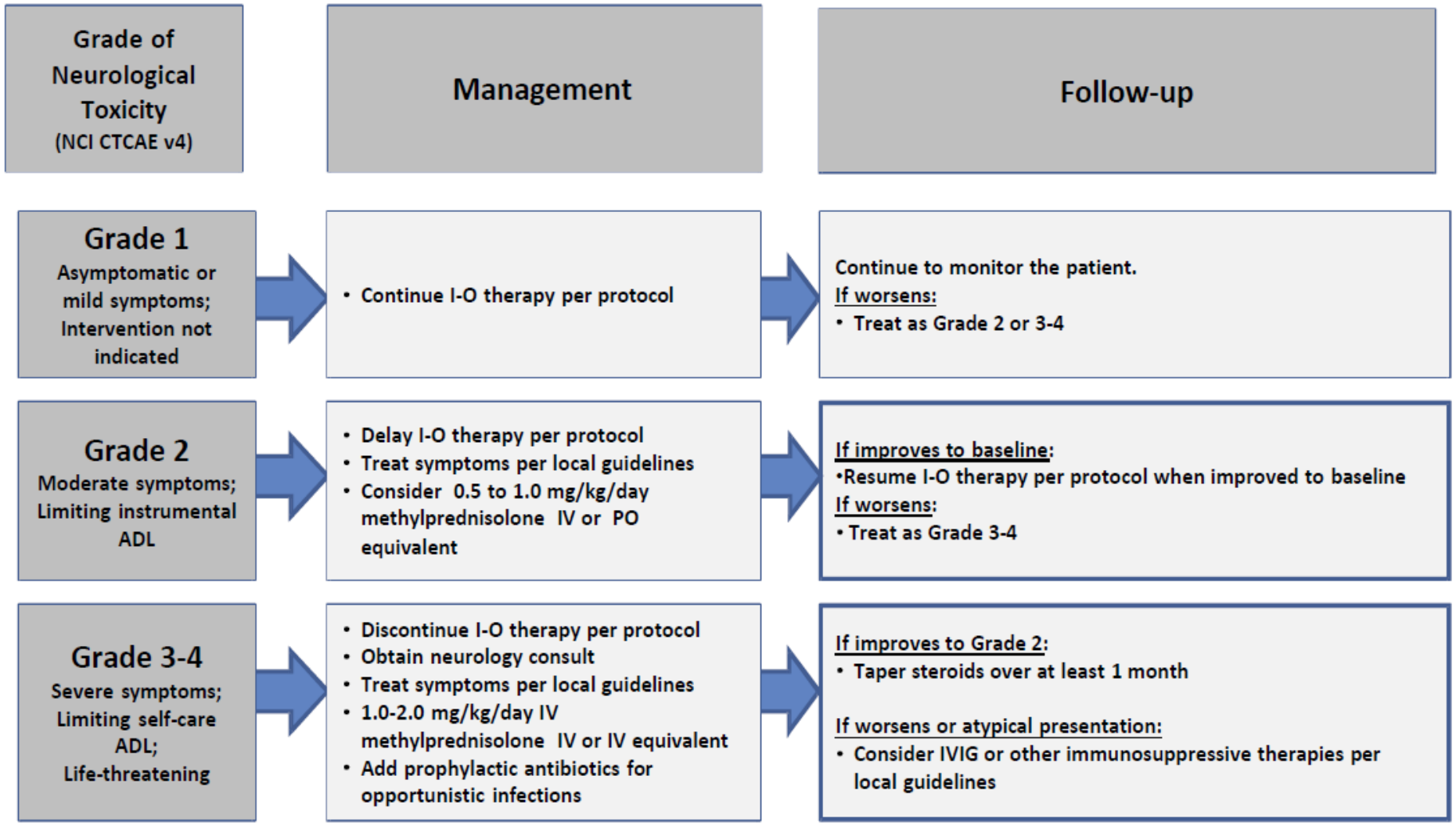
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of 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 A-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 A).
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
1L	first-line
2L	second-line
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibody(ies)
ADP	adenosine diphosphate
AE(s)	adverse event(s)
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
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
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
CNS	central nervous system

Abbreviation	Definition
CR	complete response
CRC	colorectal cancer
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DCR	disease control rate
DLT	dose limiting toxicity
dMMR	mismatch repair deficient
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
EPO	erythropoietin
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GnRH	gonadotropin-releasing hormone
HCC	hepatocellular carcinoma
HIV	human immunodeficiency virus
I/E	inclusion/exclusion
IB	Investigator's Brochure
ICF	informed consent form
IgG4	immunoglobulin G4
IL-2	interleukin 2
IL-2Rαβγ	IL-2 receptor alpha beta gamma
IL-2Rβγ	IL-2 receptor beta gamma
imAE(s)	immune-mediated AE(s)
INR	international normalized ratio
irAE(s)	immune-related AE(s)
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IV	intravenous(ly)
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
mCRPC	metastatic castration-resistant prostate cancer
MDSC(s)	myeloid-derived suppressor cell(s)
MedDRA	Medical Dictionary for Regulatory Activities
MSI-H	microsatellite instability-high

Abbreviation	Definition
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCI	National Cancer Institute
NK	natural killer
NKTR-214-AC	NKTR-214 active cytokines
NKTR-214-RC	NKTR-214 related cytokines
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
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programed cell death ligand 1
PEG	polyethylene glycol
PI	Principal Investigator
PK	pharmacokinetics
PORTER	Prostate Researching Translational Endpoints Correlated to Response
PPK	population pharmacokinetics
PR	partial response
PSA	prostate-specific antigen
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q3M	every 3 months
Q3W	every 3 weeks
Q4W	every 4 weeks
QTcF	Fridericia's corrected QT interval
RBC	red blood cell
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
rhIL-2	recombinant human interleukin-2
rPFS	radiographic progression-free survival
S	screening
SAC	Safety Assessment Committee
SAE(s)	serious adverse event(s)

Abbreviation	Definition
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SJS	Stevens-Johnson syndrome
SOA	Schedule of Activities
TB	tuberculosis
TEN	toxic epidermal necrolysis
Tmax	mean time to maximum serum concentration
TMB	tumor mutational burden
TNBC	triple-negative breast cancer
TRAE(s)	treatment-related adverse event(s)
Treg(s)	regulatory tumor cell(s)
TSH	thyroid stimulating hormone
UC	urothelial carcinoma
ULN	upper limit of normal
US	United States
USPI	US Prescribing Information
WBC	white blood cell

10.3 APPENDIX A-3: APPENDIX COHORT A AMENDMENT HISTORY

DOCUMENT HISTORY	
Documents	**Date of Issue**
Amendment 1	24 Jan 2019
Original Appendix Cohort A	07 Dec 2018

11 REFERENCES

Addendum 1 to NKTR-214 Investigator's Brochure version 5.0, dated 03-Jul-2018. Nektar Therapeutics, 29-Aug-2018.

Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SAJR, Behjati S, Biankin AV, et al. Signatures of mutational processes in human cancer. Nature 2013;500(7463):415–21.

Boyman O, Sprent J. The role of interleukin-2 during homeostasis and activation of the immune system. Nat Rev Immunol 2012;12(3):180–90.

Charych DH, Hoch U, Langowski JL, Lee SR, Addepalli MK, Kirk PB, et al. NKTR-214, an engineered cytokine with biased IL2 receptor binding, increased tumor exposure, and marked efficacy in mouse tumor models. Clin Cancer Res 2016a;22(3):680–90.

Charych DH, Rubas W, Dixit V, Cetz J, Pena R, Langowski JL, et al. Immune memory in nonclinical models after treatment with NKTR-214, an engineered cytokine biased towards expansion of CD8+ T cells in tumor. Presented at: American Society of Clinical Oncology 2016 Annual Meeting; June 3-7, 2016; Chicago, IL. J Clin Oncol 2016b;34(15_suppl; abstract 11545). Available at: https://meetinglibrary.asco.org/record/126793/abstract. Accessed on 18-Oct-2018.

Charych D, Khalili S, Dixit V, Kirk P, Chang T, Langowski J, et al. Modeling the receptor pharmacology, pharmacokinetics, and pharmacodynamics of NKTR-214, a kinetically-controlled interleukin-2 (IL2) receptor agonist for cancer immunotherapy. PLoS ONE 2017;12(7):e0179431.

De Marzo AM, Platz EA, Sutcliffe S, Xu J, Grönberg H, Drake CG, et al. Inflammation in prostate carcinogenesis. Nat Rev Cancer 2007;7(4):256–69.

Diab A, Tannir NM, Bernatchez C, Haymaker CL, Bentebibel SE, Curti BD, et al. A phase 1/2 study of a novel IL-2 cytokine, NKTR-214, and nivolumab in patients with select locally advanced or metastatic solid tumors. Presented at: American Society of Clinical Oncology 2017 Annual Meeting; June 2-6. 2017; Chicago, IL. J Clin Oncol 2017a;35(15_suppl; abstract e14040). Available at: https://meetinglibrary.asco.org/record/149613/abstract. Accessed on 18-Oct-2018.

Diab A, Tannir N, Cho D, Papadimitrakopoulou V, Bernatchez C, Haymaker C, et al. Pivot-02: Preliminary safety, efficacy and biomarker results from dose escalation of the Phase 1/2 study of CD-122-biased agonist NKTR-214 plus nivolumab in patients with locally advanced/metastatic melanoma, renal cell carcinoma and non-small cell lung cancer. Presented at: Society for Immunotherapy of Cancer 2017; November 8-12, 2017b; National Harbor, MD. Available at: http://www.nektar.com/application/files/8115/1042/7902/SITC2017_-Oral_Session_207_-_PIVOT-02_-_Adi_Diab-preso.pdf. Accessed on 22-Mar-2018.

Diab A, Hurwitz M, Cho D, Papadimitrakopoulou V, Curti B, Tykodi S, et al. NKTR-214 (CD-122-biased agonist) plus nivolumab in patients with advanced solid tumors: Preliminary phase 1/2 results of PIVOT. Presented at: American Society of Clinical Oncology; June 1-5, 2018; Chicago, IL. Available at: https://www.nektar.com/application/files/1815/2797/2670/NKTR-214_Oral_Presentation_ASCO_02Jun2018-Final.pdf. Accessed on 04-Oct-2018.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228–47.

Flammiger A, Bayer F, Cirugeda-Kühnert A, Huland H, Tennstedt P, Simon R, et al. Intratumoral T but not B lymphocytes are related to clinical outcome in prostate cancer. APMIS 2012;120(11):901–8.

Graff JN, Alumkal JJ, Drake CG, Thomas GV, Redmond WL, Farhad M, et al. Early evidence of anti-PD-1 activity in enzalutamide-resistant prostate cancer. Oncotarget 2016;7(33):52810–7.

Kwon ED, Drake CG, Scher HI, Fizazi K, Bossi A, van den Eertwegh AJM, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 2014;15(7):700–12.

Lopez-Bujanda Z, Drake CG. Myeloid-derived cells in prostate cancer progression: phenotype and prospective therapies. J Leukoc Biol 2017;102(2):393–406.

Martin AM, Nirschl TR, Nirschl CJ, Francica BJ, Kochel CM, van Bokhoven A, et al. Paucity of PD-L1 expression in prostate cancer: Innate and adaptive immune resistance. Prostate Cancer Prostatic Dis 2015;18(4):325–32.

Massari F, Ciccarese C, Caliò A, Munari E, Cima L, Porcaro AB, et al. Magnitude of PD-1, PD-L1 and T lymphocyte expression on tissue from castration-resistant prostate adenocarcinoma: An exploratory analysis. Target Oncol 2016;11(3):345–51.

McDermott DF, Cheng S-C, Signoretti S, Margolin KA, Clark JI, Sosman JA, et al. The high-dose aldesleukin "select" trial: A trial to prospectively validate predictive models of response to treatment in patients with metastatic renal cell carcinoma. Clin Cancer Res 2015;21(3):561–8.

Miller AM, Lundberg K, Ozenci V, Banham AH, Hellström M, Egevad L, et al. CD4+CD25high T cells are enriched in the tumor and peripheral blood of prostate cancer patients. J Immunol 2006;177(10):7398–405.

Nivolumab Investigator's Brochure version 17, dated 27-Jun-2018. Bristol-Myers Squibb Research and Development, 2018. Document Control No. 930038243.

NKTR-214 Investigator's Brochure version 5.0, dated 03-Jul-2018. Nektar Therapeutics, 2018.

Opdivo (nivolumab) US Prescribing Information (USPI), Nov-2018; Bristol-Myers Squibb Company, Princeton, NJ.

Pasero C, Gravis G, Guerin M, Granjeaud S, Thomassin-Piana J, Rocchi P, et al. Inherent and tumor-driven immune tolerance in the prostate microenvironment impairs natural killer cell antitumor activity. Cancer Res 2016;76(8):2153–65.

Payne R, Glenn L, Hoen H, Richards B, Smith JW, Lufkin R, et al. Durable responses and reversible toxicity of high-dose interleukin-2 treatment of melanoma and renal cancer in a Community Hospital Biotherapy Program. J Immunother Cancer 2014;2:13.

Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial design and objectives for castration-resistant prostate cancer: Updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol 2016;34(12):1402–18.

Sfanos KS, Bruno TC, Meeker AK, De Marzo AM, Isaacs WB, Drake CG. Human prostate-infiltrating CD8+ T lymphocytes are oligoclonal and PD-1+. Prostate 2009;69(15):1694–703.

Study 15-214-01 (EXCEL; NCT02869295): A Phase 1/2 Multicenter Dose Escalation and Expansion Study of NKTR-214 in Subjects with Locally Advanced or Metastatic Solid Tumors (NKTR-214). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02869295. Accessed on 09-Oct-2018.

Study 16-214-02 (PIVOT-02; NCT02983045): A Dose Escalation and Cohort Expansion Study of CD122-Biased Cytokine (NKTR-214) in Combination with Anti-PD-1 Antibody (Nivolumab) in Patients with Select Advanced or Metastatic Solid Tumors. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02983045. Accessed on 09-Oct-2018.

Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366(26):2443–54.