SARAH CANNON
Development Innovations

# BMT 24

# A Phase II Single Arm Study of Nivolumab as Maintenance Therapy after Autologous Stem Cell Transplantation in Patients with Hodgkin Lymphoma at Risk of Relapse or Progression

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| **SARAH CANNON DEVELOPMENT INNOVATIONS STUDY NUMBER:** | BMT 24 |
| **STUDY DRUG:** | Nivolumab |
| **SPONSOR:** | Sarah Cannon Development Innovations, LLC<br>1100 Dr. Martin L. King Jr. Blvd., Suite 800<br>Nashville, TN 37203<br>1-844-710-6157<br>asksarah@sarahcannon.com |
| **STUDY CHAIR:** | Carlos Bachier, MD<br>Sarah Cannon Research Institute<br>1100 Dr. Martin L. King Jr. Blvd., Suite 800<br>Nashville, TN 37203<br>1-844-710-6157 |
| **DATE FINAL:** | 06 July 2017 |

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| **AMENDMENT NUMBER:** | 1 | **AMENDMENT DATE:** | 23 August 2017 |
| **AMENDMENT NUMBER:** | 2 | **AMENDMENT DATE:** | 16 October 2017 |
| **AMENDMENT NUMBER:** | 3 | **AMENDMENT DATE:** | 23 March 2018 |
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| **AMENDMENT NUMBER:** | 5 | **AMENDMENT DATE:** | 16 January 2019 |
| **AMENDMENT NUMBER:** | 6 | **AMENDMENT DATE:** | 07 February 2020 |

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**This clinical study shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:**

- **International Council for Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards**
  - **Title 21CFR Part 312, Investigational New Drug Application**
  - **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**

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# Clinical Study Signature Approval Page

## A Phase II Single Arm Study of Nivolumab as Maintenance Therapy after Autologous Stem Cell Transplantation in Patients with Hodgkin Lymphoma at Risk of Relapse or Progression

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|---|---|---|
| Carlos Bachier, M.D. | I am approving this document. | 02/12/2020 09:38 AM EST |
| **Study Chair**<br>**Sarah Cannon Research Institute** | **Study Chair Signature** | **Date** |
| Sheetal Khedkar, M.D., MSPH | I am approving this document. | 02/13/2020 08:51 AM EST |
| **Sponsor Representative**<br>**Sarah Cannon Development Innovations, LLC** | **Sarah Cannon Development Innovations, LLC Representative Signature** | **Date** |

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## Clinical Study Principal Investigator Signature Form

## A Phase II Single Arm Study of Nivolumab as Maintenance Therapy after Autologous Stem Cell Transplantation in Patients with Hodgkin Lymphoma at Risk of Relapse or Progression

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By signing this protocol acceptance page, I confirm I have read, understand, and agree to conduct the study in accordance with the current protocol.

| _____ | _____ | _____ |
|---|---|---|
| **Principal Investigator Name** (Please Print) | **Principal Investigator Signature** | **Date** |

Please retain a copy of this page for your study files and return the original signed and dated form to:

Sarah Cannon Development Innovations, LLC
1100 Dr. Martin L. King Jr. Blvd., Suite 800
Attn: BMT 24 Study Team
Nashville, TN 37203

SARAH CANNON
Development Innovations

## BMT 24 Summary of Change

| AMENDMENT NUMBER: | 6 | AMENDMENT DATE: | 07 February 2020 |
|---|---|---|---|

**Section 5.0 Study Design** Five of the forty patients to be enrolled on the study will be enrolled to a control group.

**Section 5.4.2 Immune Recovery versus Control Group** Section added to detail study schedule for control patients.

# BMT 24 PROTOCOL SYNOPSIS

| | | |
|---|---|---|
| **Title of Study:** | A Phase II Single Arm Study of Nivolumab as Maintenance Therapy after Autologous Stem Cell Transplantation in Patients with Hodgkin Lymphoma at Risk of Relapse or Progression | |
| **Sarah Cannon Development Innovations Study Number:** | BMT 24 | |
| **Sponsor:** | Sarah Cannon Development Innovations, LLC – Nashville, TN | |
| **Study Duration:** | The total duration of the study is planned to be 4 years (2 years enrollment and 2 years maximum follow-up). | **Phase of Study:** II |
| **Study Centers:** | This study will be conducted at 6 study sites. | |
| **Number of Patients:** | Up to 40 patients are planned to be enrolled in this study: 35 will receive study treatment and 5 patients will receive standard-of-care procedures and treatment both pre- and post-transplant. | |
| **Objectives:** | **Primary Objective**<br>The primary objective of this study is to:<br>• Evaluate safety and tolerability of nivolumab as maintenance early after autologous stem cell transplant (ASCT) in patients with Hodgkin Lymphoma (HL)<br>**Secondary Objectives**<br>The secondary objective of this study is to:<br>• Evaluate PFS at 12 months post-transplant when nivolumab is administered as maintenance in patients with HL after ASCT<br>**Exploratory Objectives**<br>The exploratory objectives of this study are to:<br>• Correlate efficacy of nivolumab when given as maintenance after ASCT with programmed cell death protein-1 (PD-1) expression and other immune effector and regulatory cells<br>• Correlate positron emission tomography (PET)- computed tomography (CT) negativity with PFS | |
| **Study Design:** | This is a Phase II single-arm open-label study of nivolumab as maintenance therapy after ASCT in patients with HL at risk of relapse or progression. | |
| **Study Drugs, Doses, and Modes of Administration:** | Patients will receive nivolumab (240 mg IV) starting Day 45-180 post-transplant (±10 days) every 2 weeks for up to a maximum of 6 months of treatment. Five patients will receive standard-of-care treatment pre- and post-transplant as a control group to compare immune recovery. | |

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| **Inclusion Criteria:** | 1. Patients 18 years of age and older with HL who have received auto-HSCT in the previous 45-180 days.<br>2. Complete response (CR), partial response (PR) or stable disease (SD) to salvage therapy prior to ASCT<br>3. High risk of residual HL post-ASCT, as determined by one of the following:<br>• Positive PET scan defined by the Deauville scale 3-4 (Appendix C) and within 2 months of start of high-dose chemotherapy prior to ASCT<br>• Refractory to frontline therapy<br>• Relapse <12 months after frontline therapy<br>• Relapse ≥12 months after frontline therapy with extranodal disease<br>4. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0-1 (Appendix A).<br>5. Adequate hematologic function defined as all of the following:<br>– Absolute neutrophil count (ANC) ≥1000/μL<br>– Hemoglobin (Hgb) ≥8 g/dL (transfusions to reach this point are not permitted)<br>– Platelets ≥50,000/μL (transfusion is not permitted)<br>6. Adequate liver function defined as all of the following:<br>– Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × the upper limit of normal (ULN)<br>– Total bilirubin ≤1.5 × ULN (unless the patient has Grade 1 bilirubin elevation due to Gilbert disease or a similar syndrome involving slow conjugation of bilirubin)<br>7. Adequate renal function defined as serum creatinine ≤1.5 mg/dL (133 μmol/L).<br>8. Females of childbearing potential must have a negative serum or urine pregnancy test result within 72 hours prior to the first dose of nivolumab and must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab and for 7 months following their last dose of study drug (Appendix C). Females of non-childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy.<br>**9.** Male patients with female partners of childbearing potential and women patients of childbearing potential are required to use two forms of **acceptable** contraception, including one barrier method, during their participation in the study and for 7 months following last dose of study drug. Male patients must also refrain from donating sperm during their participation in the study and for 7 months following last dose of study drug (Appendix C).<br>10. Willingness and ability to comply with study and follow-up procedures.<br>11. Ability to understand the nature of this study and give written informed consent. |

# BMT 24 PROTOCOL SYNOPSIS

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| **Exclusion Criteria:** | 1. Patients that have received an allogenic transplant.<br>2. Prior ASCT or current therapy with other anti-neoplastic or investigational agents.<br>3. Best response of progressive disease prior to ASCT<br>4. Patients with any autoimmune disease or a history of autoimmune disease. Patients with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.<br>5. Any condition requiring systemic treatment with corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days prior to first dose of study drug. Inhaled steroids and adrenal replacement steroid doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.<br>6. Use of a study drug ≤21 days or 5 half-lives (whichever is shorter) prior to the first dose of nivolumab. For study drugs for which 5 half-lives is ≤21 days, a minimum of 10 days between termination of the study drug and administration of nivolumab is required.<br>7. Wide-field radiotherapy (including therapeutic radioisotopes such as strontium 89) administered ≤28 days or limited field radiation for palliation ≤7 days prior to starting study drug or has not recovered from side effects of such therapy.<br>8. Major surgical procedures ≤28 days of beginning study drug, or minor surgical procedures ≤7 days. No waiting required following port-a-cath placement.<br>9. Previously untreated brain metastases. Patients who have received radiation or surgery for brain metastases are eligible if therapy was completed at least 2 weeks prior to study entry and there is no evidence of central nervous system disease progression, mild neurologic symptoms, and no requirement for chronic corticosteroid therapy.<br>10. Pregnant or lactating<br>11. Acute or chronic liver, renal, or pancreatic disease.<br>12. Uncontrolled diabetes mellitus (fasting blood glucose >250 mg/dL).<br>13. Any of the following cardiac diseases currently or within the last 6 months:<br>– Left ventricular ejection fraction (LVEF) <45% as determined by multiple gated acquisition (MUGA) scan or echocardiogram (ECHO)<br>– Corrected QT (QTc) interval >480 ms on screening electrocardiogram (ECG)<br>– Unstable angina pectoris<br>– Congestive heart failure (New York Heart Association (NYHA) ≥ Grade 2 [Appendix B])<br>– Acute myocardial infarction<br>– Conduction abnormality not controlled with pacemaker or medication<br>– Significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible)<br>– Valvular disease with significant compromise in cardiac function<br>14. Inadequately controlled hypertension (i.e., systolic blood pressure [SBP] >180 mmHg or diastolic blood pressure (DBP) >100 mmHg) (patients with values above these levels must have their blood pressure [BP] controlled with medication prior to starting treatment).<br>15. Serious active infection at the time of treatment or another serious underlying medical condition that would impair the ability of the patient to receive protocol treatment. |

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| **Exclusion Criteria:** | 16. Known diagnosis of human immunodeficiency virus, hepatitis B, or hepatitis C. Testing at baseline is not required.<br>17. Presence of other active cancers, or history of treatment for invasive cancer ≤5 years. Patients with Stage I cancer who have received definitive local treatment and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (i.e., non-invasive) are eligible, as are patients with history of non-melanoma skin cancer.<br>18. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol. |
| **Statistical Methodology:** | The null hypothesis to be tested is that the true 12-month PFS is 50% against a two-sided alternative hypothesis of a 70% PFS rate. The 50% 6-month PFS rate was obtained from Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (Cheson et al. 2014, see Appendix F). A two-sided, one-sample log-rank test calculated from a sample of 36 evaluable subjects achieves 80.3% power at a 0.050 significance level to detect an improvement of 20% in 12-month PFS.<br><br>The probability that a subject experiences an event during the study is 0.4579. The expected number of events during the study is 16. It is assumed that the survival time distributions of both groups are approximated reasonably well by the Weibull distribution with a shape parameter of 1.00. These proportions assume an enrollment period of 18 months and a follow-up period of 12 months after the last subject is added. In order to allow for a 10% dropout rate, a total of 40 patients will be enrolled. The sample size was calculated using PASS version 14. |

# BMT 24 CONTACT INFORMATION

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|---|---|
| **Sarah Cannon Development Innovations Contact Information:** | Sarah Cannon Development Innovations<br>1100 Dr. Martin L. King Jr. Blvd., Suite 800<br>Nashville, TN 37203<br>1-844-710-6157<br>asksarah@sarahcannon.com |
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# LIST OF ABBREVIATIONS

| | |
|---|---|
| **AE** | Adverse event |
| **ALP** | Alkaline phosphatase |
| **ALT (SGPT)** | Alanine aminotransferase |
| **ANC** | Absolute neutrophil count |
| **ASCT** | Autologous stem cell transplant |
| **AST (SGOT)** | Aspartate aminotransferase |
| **CBC** | Complete blood count |
| **CFR** | Code of Federal Regulations |
| **cHL** | Classical Hodgkin Lymphoma |
| **CI** | Confidence interval |
| **CMP** | Comprehensive metabolic profile |
| **CR** | Complete response/remission |
| **CRF** | Case report form |
| **CT** | Computed tomography |
| **ECG** | Electrocardiogram |
| **ECOG** | Eastern Cooperative Oncology Group |
| **eCRF** | Electronic case report form |
| **EFS** | Event-free survival |
| **FDA** | Food and Drug Administration |
| **GCP** | Good Clinical Practice |
| **HIPAA** | Health Insurance Portability and Accountability Act |
| **HL** | Hodgkin Lymphoma |
| **HSCT** | Hematopoietic stem cell transplantation |
| **IB** | Investigator Brochure |
| **ICF** | Informed consent form |
| **ICH** | International Council for Harmonisation |
| **INR** | International normalized ratio |
| **IRB** | Institutional Review Board |
| **IV** | Intravenously |
| **NCI CTCAE** | National Cancer Institute Common Terminology Criteria for Adverse Events |
| **NSCLC** | Non-small cell lung cancer |
| **OS** | Overall survival |
| **PD-1** | Programmed cell death protein-1 |
| **PET** | Positron emission tomography |
| **PFS** | Progression-free survival |
| **PHI** | Protected health information |
| **PK** | Pharmacokinetics |

## LIST OF ABBREVIATIONS (continued)

| | |
|---|---|
| **PR** | Partial response/remission |
| **RCC** | Renal cell cancer |
| **SAE** | Serious adverse event |
| **SAR** | Suspected adverse reaction |
| **SD** | Stable disease |
| **SUSAR** | Suspected unexpected serious adverse reaction |
| **ULN** | Upper limit of normal |

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# 1. INTRODUCTION

## 1.1 Background

Hodgkin Lymphoma (HL) is a cancer that arises from germinal center or post-germinal center B cells. The disease has unique cellular composition distinguishing it from other B cell lymphomas and consists of small numbers of malignant Reed-Sternberg cells within an extensive but ineffective inflammatory and immune-cell infiltrate. Hodgkin Lymphoma accounts for approximately 10% of all lymphomas, leading to about 8500 new cases and 1120 deaths annually in the United States (Siegel et al. 2016). Hodgkin Lymphoma has a bimodal age distribution curve with a peak in young adults at approximately 20 years of age and in older adults around age 65 (Ries et al. 1997). Most patients affected by this disease are young adults.

## 1.2 Treatment of Relapsed or Refractory Hodgkin Lymphoma

The majority of patients with HL are cured with combination chemotherapy and/or radiation therapy with complete remission attained in >80% of patients. High-dose therapy and autologous stem cell transplant (ASCT) are used as standard of care for patients with primary resistant or recurrent HL. While transplant results in a cure for some patients, more than 50% will eventually relapse and die of the disease (Majhail et al. 2006). Prognostic factors have been identified that affect long-term outcomes after transplant for patients with Hodgkin disease. Time-to-treatment failure has been found to be adversely influenced by advanced stage at diagnosis, complementary radiotherapy before ASCT, a short first complete response, and detectable disease at ASCT (Sureda et al. 2005). Patients who progress after ASCT have limited therapeutic options to improve the outcome of their disease.

## 1.3 Prognostic Factors in Hodgkin Lymphoma

Prognostic factors have been identified that affect long-term outcome after transplant for patients with Hodgkin disease. Poor outcomes post-ASCT are associated with the presence of B symptoms, extranodal disease, and a less than 12 month duration of remission after frontline chemotherapy. Patients with intermediate or high-risk disease have a 5-year event-free survival (EFS) rate of less than 30% compared to 65% to 80% for patients with low-risk disease (Moskowitz et al. 2001, Majhail et al. 2006), (Sureda et al. 2005). Patients who progress after ASCT have limited therapeutic options to improve the outcome of their disease. Most relapses occur within the first 2 years post-ASCT. Introducing a novel therapy to prevent disease progression and/or relapse in intermediate- to high-risk patients post-ASCT would be of benefit for these patients.

## 1.4 Post-transplant Therapy for Hodgkin Lymphoma

Based on data in the AETHERA trial, in August 2015 the FDA approved brentuximab vedotin for the post-autologous hematopoietic stem cell transplantation (auto-HSCT) treatment of patients with classical HL at high risk of relapse or progression. Progression-free survival (PFS) in the brentuximab vedotin arm was 42.9 months compared to 24.1 months in the placebo arm (Moskowitz et al. 2015). While leading to a significant improvement in PFS, discontinuation of

treatment due to adverse events occurred in over 30% of patients primarily due to peripheral sensory and motor neuropathies (Moskowitz et al. 2015). This intolerance to the only established therapy to prevent relapse demonstrates the need for the development of novel treatment options for these patients.

## 1.5 Nivolumab

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes (Sharpe et al. 2007). Binding of PD-1 to its ligands, programmed death-ligand 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

The pharmacokinetics (PK), clinical activity, and safety of nivolumab have been assessed in subjects with non-small cell lung cancer (NSCLC), melanoma, clear-cell renal cell carcinoma (RCC), and classical Hodgkin Lymphoma (cHL) in addition to other tumor types. Nivolumab monotherapy is approved in multiple countries, including the US and EU, for unresectable or metastatic melanoma, previously treated metastatic NSCLC, and previously treated advanced RCC. In addition, nivolumab is also approved for the treatment of cHL in the US.

### 1.5.1 Clinical Efficacy

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy and in combination with ipilimumab in several tumor types, including NSCLC, melanoma, RCC, cHL, SCLC, gastric cancer, urothelial cancer, hepatocellular carcinoma, and colorectal cancer. In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in overall survival (OS) compared with the current standard of care in subjects with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or squamous cell carcinoma of the head and neck (SCCHN).

#### 1.5.1.1 Clinical Efficacy in Hodgkin Lymphoma

Nivolumab monotherapy has demonstrated clinical benefit in subjects with cHL who have relapsed or progressed, including those who received autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin, and has been approved for use in the US. Two studies evaluated the efficacy of nivolumab as a single agent in patients with cHL after failure of autologous HSCT and post-transplantation brentuximab vedotin. Patients received 240 mg of nivolumab administered intravenously (IV) over 60 minutes every 2 weeks until disease progression, maximal clinical benefit, or unacceptable toxicity. A cycle consisted of one dose. Dose reduction was not permitted.

Efficacy was evaluated in 95 patients (both trials combined) who had received brentuximab vedotin after failure of autologous HSCT. Response was assessed using the Revised Response

Criteria for Malignant Lymphoma (Cheson et al. 2007). Seven patients (7%) had complete remission (CR) with a 95% confidence interval (CI, [3, 1]) and 55 (58%) patients had partial remission (PR) with a 95% CI (47, 68). The objective response rate (CR + PR) was 62 patients (65%). Median duration of response (DoR) was 8.7 months and median time to response was 2.1 months.

### 1.5.2 Clinical Safety

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 12,300 subjects treated to date. For monotherapy, the safety profile is similar across tumor types. There is no pattern in the incidence, severity, or causality of adverse events (AEs) to nivolumab dose level. In Phase 3 controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical efficacy and manageable using established safety guidelines. Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and timely immunosuppressive therapy or other supportive care.

#### 1.5.2.1 Renal and Hepatic Impairment

The effect of renal impairment on the clearance (CL) of nivolumab was evaluated in subjects with mild (glomerular filtration rate [GFR] <90 and ≥60 mL/min/1.73 $m^2$; n=379), moderate (GFR <60 and ≥30 mL/min/1.73 $m^2$; n=179), or severe (GFR <30 and ≥15 mL/min/1.73 $m^2$; n=2) renal impairment compared to subjects with normal renal function (GFR ≥90 mL/min/1.73 $m^2$; n=342) in the population pharmacokinetic (PPK) analysis. No clinically important differences in the CL of nivolumab were found between subjects with mild or moderate renal impairment and subjects with normal renal function. Data from subjects with severe renal impairment are too limited to draw conclusions on this population.

The effect of hepatic impairment on the CL of nivolumab was evaluated in subjects with mild hepatic impairment (total bilirubin 1.0 to 1.5 times upper limit of normal [ULN] or aspartate aminotransferase [AST] > ULN as defined using the National Cancer Institute [NCI] criteria of hepatic dysfunction; n=92) compared to subjects with normal hepatic function (total bilirubin and AST ≤ ULN; n=804) in the population PK analyses. No clinically important differences in the CL of nivolumab were found between subjects with mild hepatic impairment and normal hepatic function. Nivolumab has not been studied in subjects with moderate (total bilirubin >1.5 to 3 times ULN and any AST) or severe hepatic impairment (total bilirubin >3 times ULN and any AST).

## 1.6 PD-1 Expression in Hodgkin Lymphoma

Studies have found high expression of PD-L1 in HL (Roemer et al 2016). Programmed cell death protein 1 (PD-1) blockade with nivolumab in clinical trials enrolling heavily pre-treated HL patients have resulted in response rates in over 85% of patients (Ansell et al. 2015). The most common drug-related AEs were rash and decreased platelet count with 9% of patients discontinuing due to toxic effects (Ansell et al. 2015). Data demonstrating the tolerability and

efficacy of PD-1 inhibition in HL patients make nivolumab a promising therapy to evaluate in the post-transplant setting.

### 1.7 Rationale for the Study

The malignant Reed-Sternberg cells found in HL have been found to overexpress PD-1 (Green et al. 2010). Nivolumab, an antibody directed against PD-1, has been well-tolerated and efficacious in this patient population (Ansell et al. 2015). We propose to study nivolumab maintenance therapy post-ASCT in Hodgkin disease to see if it is well-tolerated when given as early maintenance therapy. Moskowitz et al. 2010 conducted a study to identify prognostic factors for patients with relapsed or refractory HL receiving transplant. In this analysis of 153 patients, it was found that functional imaging status before ASCT was the only factor significant for EFS and OS and clearly identified a poor risk population (5 year EFS 31% and 75% for FI-positive and negative patients respectively). This study aims to enroll high-risk patients as defined by this manuscript to receive nivolumab therapy as consolidation therapy post-transplant. We are also exploring if PFS can be prolonged in high-risk HL patients compared to historical placebo controls reported in other studies.

## 2. STUDY OBJECTIVES

### 2.1 Primary Objective

The primary objective of this study is to:

- Evaluate safety and tolerability of nivolumab as maintenance therapy early after ASCT in patients with HL

### 2.2 Secondary Objectives

The secondary objective of this study is to:

- Evaluate PFS at 12 months post-transplant when nivolumab is administered as maintenance therapy in patients with HL after ASCT

### 2.3 Exploratory Objectives

The exploratory objectives of this study are to:

- Correlate efficacy of nivolumab when given as maintenance therapy after ASCT with PD-1 expression and other immune effector and regulatory cells
- Correlate positron emission tomography (PET)-computed tomography (CT) negativity with PFS

### 2.4 Endpoints

#### 2.4.1 Safety Endpoints

- Type, incidence, severity, seriousness, and relatedness of AEs
- Laboratory abnormalities

- AEs leading to discontinuation

### 2.4.2 Efficacy Endpoint

- Progression-free survival

### 2.4.3 Additional Endpoint

- PET-CT negativity at 1 year post-transplant

## 3. STUDY PATIENT POPULATION AND DISCONTINUATION

### 3.1 Inclusion Criteria

Patients who will receive study drug must meet the following criteria in order to be included in the research study:

1. Patients 18 years of age and older with HL who have received auto-HSCT in the previous 45-180 days.
2. Complete response (CR), partial response (PR) or stable disease (SD) to salvage therapy prior to ASCT
3. High risk of residual HL post-ASCT, as determined by 1 of the following:
    - Positive PET scan defined by the Deauville scale 3-4 (Appendix C) and within 2 months of start of high-dose chemotherapy prior to ASCT
    - Refractory to frontline therapy
    - Relapse <12 months after frontline therapy
    - Relapse ≥12 months after frontline therapy with extranodal disease
4. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 - 1 (Appendix A).
5. Adequate hematologic function defined as all of the following:
    - Absolute neutrophil count (ANC) ≥1000/µL
    - Hemoglobin (Hgb) ≥8 g/dL (transfusions to reach this point are not permitted)
    - Platelets ≥50,000/µL (transfusion is not permitted)
6. Adequate liver function defined as all of the following:
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × the upper limit of normal (ULN)
    - Total bilirubin ≤1.5 × ULN (unless the patient has Grade 1 bilirubin elevation due to Gilbert disease or a similar syndrome involving slow conjugation of bilirubin)
7. Adequate renal function defined as serum creatinine ≤1.5 mg/dL (133 µmol/L)

8. Females of childbearing potential must have a negative serum or urine pregnancy test result within 72 hours prior to the first dose of nivolumab and must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab and for 7 months following their last dose of study drug (Appendix D). Females of non-childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy.
9. Male patients with female partners of childbearing potential and women patients of childbearing potential are required to use two forms of **acceptable** contraception, including one barrier method, during their participation in the study and for 7 months following last dose of study drug. Male patients must also refrain from donating sperm during their participation in the study and for 7 months following last dose of study drug (Appendix D).
10. Willingness and ability to comply with study and follow-up procedures.
11. Ability to understand the nature of this study and give written informed consent.

### 3.2 Exclusion Criteria

Patients who will receive study drug who meet any of the following criteria will be excluded from study entry:

1. Patients that have received an allogenic transplant
2. Prior allogeneic stem cell transplant or current therapy with other anti-neoplastic or investigational agents
3. Best response of progressive disease prior to ASCT
4. Patients with any autoimmune disease or a history of autoimmune disease. Patients with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
5. Any condition requiring systemic treatment with corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days prior to first dose of study drug. Inhaled steroids and adrenal replacement steroid doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
6. Use of a study drug ≤21 days or 5 half-lives (whichever is shorter) prior to the first dose of nivolumab. For study drugs for which 5 half-lives is ≤21 days, a minimum of 10 days between termination of the study drug and administration of nivolumab is required.
7. Wide-field radiotherapy (including therapeutic radioisotopes such as strontium 89) administered ≤28 days or limited field radiation for palliation ≤7 days prior to starting study drug or has not recovered from side effects of such therapy.
8. Major surgical procedures ≤28 days of beginning study drug, or minor surgical procedures ≤7 days. No waiting required following port-a-cath placement.

9. Previously untreated brain metastases. Patients who have received radiation or surgery for brain metastases are eligible if therapy was completed at least 2 weeks prior to study entry and there is no evidence of central nervous system disease progression, mild neurologic symptoms, and no requirement for chronic corticosteroid therapy.
10. Pregnant or lactating
11. Acute or chronic liver, renal, or pancreatic disease.
12. Uncontrolled diabetes mellitus (fasting blood glucose >250 mg/dL).
13. Any of the following cardiac diseases currently or within the last 6 months:
    - Left ventricular ejection fraction (LVEF) <45% as determined by multiple gated acquisition (MUGA) scan or echocardiogram (ECHO)
    - Corrected QT (QTc) interval >480 ms on screening electrocardiogram (ECG)
    - Unstable angina pectoris
    - Congestive heart failure (New York Heart Association (NYHA) ≥ Grade 2 [Appendix B])
    - Acute myocardial infarction
    - Conduction abnormality not controlled with pacemaker or medication
    - Significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible)
    - Valvular disease with significant compromise in cardiac function
14. Inadequately controlled hypertension (i.e., systolic blood pressure [SBP] >180 mmHg or diastolic blood pressure [DBP] >100 mmHg) (patients with values above these levels must have their blood pressure [BP] controlled with medication prior to starting treatment).
15. Serious active infection at the time of treatment, or another serious underlying medical condition that would impair the ability of the patient to receive protocol treatment.
16. Known diagnosis of human immunodeficiency virus, hepatitis B, or hepatitis C. Testing at baseline is not required.
17. Presence of other active cancers, or history of treatment for invasive cancer ≤5 years. Patients with Stage I cancer who have received definitive local treatment and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (i.e., non-invasive) are eligible, as are patients with history of non-melanoma skin cancer.
18. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.

### 3.3 Discontinuation from Study Treatment

Patients will be discontinued from study treatment for any of the following reasons:

- Disease progression
- Irreversible or intolerable toxicity or abnormal laboratory values thought to be related to drug toxicity
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness (this will be at the Investigator's discretion)
- Inability of the patient to comply with study requirements
- Patient requests to discontinue treatment
- Patient withdraws consent from the study
- Non-compliance/lost to follow-up
- Pregnancy

After discontinuation from protocol treatment, patients must be followed for AEs for 100 days after their last dose of nivolumab. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the Investigator, these values are not likely to improve, because of the underlying disease. In this case, the Investigator must record his or her reasoning for this decision in the patients' medical records.

All patients who have Grade 3 or 4 laboratory abnormalities (per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.03) at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the Investigator, not likely that these values are to improve. In this case, the Investigator must record his or her reasoning for making this decision in the patients' medical records.

## 4. PATIENT REGISTRATION

The patient must willingly consent after being informed of the procedures to be followed, experimental nature of the treatment, potential benefits, treatment alternatives, side effects, risks, and discomforts. Institutional Review Board (IRB) approval of this protocol and consent form is required. Eligible patients who wish to participate in the study will be enrolled into the study.

Registration must occur prior to the initiation of protocol therapy. Patients eligible to participate in the study may be enrolled through the Sarah Cannon Development Innovations Central Enrollment Desk. The enrollment desk may be reached by calling (844) 710-6157. Registration may be done: 1) via fax (866) 699-0258 Monday through Friday, 8:30 a.m. to 4:30 p.m., Central Standard Time, or 2) via email at CANN.SCRIInnovationsEnr@scri-innovations.com. Patient registration will be confirmed via email within 24 hours or by the next business day.

# 5. STUDY DESIGN

This is a Phase II single-arm open-label study of nivolumab as maintenance therapy after autologous stem cell transplantation in patients with HL at risk of relapse or progression.

Patients will receive nivolumab (240 mg IV) every 2 weeks (±2 days as long as interval between doses is 12-16 days) starting 45-180 days post-transplant for up to a maximum of 6 months of treatment. To compare immune recovery, a control group of 5 patients will receive standard-of-care procedures and treatment both pre- and post-transplant. Response to treatment for patients receiving study drug will be assessed 6 months and 1 year post-transplant using the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (Cheson et al. 2014, see Appendix F).

The planned enrollment for this study is 40 patients: 35 patients receiving study drug and 5 patients will receive standard-of-care procedures and treatment both pre- and post-transplant.

## 5.1 Treatment Plan

### 5.1.1 Nivolumab

Nivolumab: 240 mg IV Day 1 of every cycle (every 2 weeks)

## 5.2 Treatment Duration

Study treatment consists of a maximum of 6 months of treatment. Patients must receive at least 2 cycles of nivolumab to be evaluable for efficacy.

## 5.3 Concomitant Medications

Patients who receive study drug will be instructed not to take any additional medications during the course of the study without prior consultation with the research team. At each visit, the patient will be asked about any new medications he/she is taking or has taken after the start of the study drug.

### 5.3.1 Permitted Concomitant Medications

Premedication with anti-emetics is allowed according to standard practice guidelines.

Medications may be administered for maintenance of existing conditions prior to study enrollment or for a new condition that develops while on study, including but not limited to the following:

- Patients are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses ≤10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. Steroid treatment specified as ≤16 mg dexamethasone by mouth (PO) daily tapered in ≤4 weeks is allowed only for the treatment of brain edema.

Other medications considered necessary for the patient's safety and well-being may be given at the discretion of the Investigator with the exception of those listed in Section 5.3.2.

### 5.3.2 Prohibited Concomitant Medications

The following treatments are prohibited for patients receiving study drug while in this study:

- No other investigational therapy should be given to patients. No anticancer agents other than the study medications should be given to patients. If such agents are required for a patient, then the patient must first be withdrawn from the study.
- Immunosuppressive agents (except to treat a drug-related AE)
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 5.3.1)

## 5.4 Correlative Studies

### 5.4.1 Biomarker Analysis

Mandatory peripheral blood samples will be collected from patients receiving study drug at Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, end of treatment (EOT [6 months]), and 1 year after the first dose of nivolumab for flow cytometric analysis of PD-1 expression of circulating immune cell subsets, including lymphoid (CD4, CD8, Treg, NK, B) and myeloid cells (monocytes, MDSCs), and expression of other checkpoint receptors, such as LAG-3, TIM-3 TIGIT, or agonists such as ICOS, GITR, OX-40. These samples will be labeled with a unique study identifier and subject code in order to maintain patient confidentiality. These samples have no clinical value and will be used for research only. Information on collection, processing storage and shipment for cells and plasma/serum will be in the laboratory manual.

### 5.4.2 Immune Recovery versus Control Group

Correlative studies will compare immune recovery for 5 patients undergoing autologous stem cell transplant for HL but not receiving nivolumab (control) with patients receiving nivolumab as maintenance therapy (treatment). All pre- and post-transplant procedures in the control group will be according to standard-of-care as determined by their treating physician. When complete blood count (CBC) and comprehensive metabolic profiling (CMP) panels are collected results will be entered into the electronic case report form (eCRF) as part of the study record. Blood samples in control patients are to be collected at:

- Between days 45-180 after autologous stem cell transplant
- Every 2-4 weeks (±5 days) while receiving study treatment based on standard-of-care schedule
- At 6 months (±7 days) from first sample, and
- At 1 year (±7 days) from first sample.

### 5.4.3 Handling, Storage and Destruction of Biological Samples

Once testing has been completed, samples will be stored for an additional year beyond study completion. At this time samples will have all identifiers removed and destroyed. Samples will be thawed, decontaminated, solidified, autoclaved, and then placed into the proper biohazard waste container for further disposal.

### 5.4.4 Withdrawal of Informed Consent for Donated Biological Samples

If a patient withdraws consent to the use of mandatory biological samples, then the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, Sarah Cannon Development Innovations is not obliged to destroy the results of this research.

As collection of these biological samples is a mandatory part of the study, the patient may not continue in the study.

## 6. DOSE MODIFICATIONS

If toxicity occurs, the toxicity will be graded utilizing the NCI CTCAE v4.03 (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf), and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof.

There will be no dose reduction of nivolumab; however, treatment delays are allowed. If the toxicity does not resolve to NCI CTCAE ≤ Grade 1 after 28 days, then the patient should be withdrawn from the study and observed until resolution of the toxicity.

The dose modifications to be used in this study are presented in Table 1.

**Table 1** **Dose Level Modifications**

| Adverse Reaction | Severity* | Dose Modification |
|---|---|---|
| Colitis | Grade 2 diarrhea or colitis | Withhold dose[a] |
| | Grade 3 diarrhea or colitis | Withhold dose[a] |
| | Grade 4 diarrhea or colitis | Permanently discontinue |
| Pneumonitis | Grade 2 | Withhold dose[a] |
| | Grade 3 or 4 | Permanently discontinue |
| Hepatitis | ASTor ALT >3 and up to 5 × the ULN or total bilirubin >1.5 and up to 3 × the ULN | Withhold dose[a] |
| | AST or ALT >5 × the ULN or total bilirubin > 3 × the ULN | Permanently discontinue |
| Hypophysitis | Grade 2 or 3 | Withhold dose[a] |
| | Grade 4 | Permanently discontinue |
| Adrenal Insufficiency | Grade 2 | Withhold dose[a] |
| | Grade 3 or 4 | Permanently discontinue |
| Type 1 Diabetes Mellitus | Grade 3 hyperglycemia | Withhold dose[a] |
| | Grade 4 hyperglycemia | Permanently discontinue |
| Nephritis and Renal Dysfunction | Serum creatinine >2.5 and up to 6 × the ULN | Withhold dose[a] |
| | Serum creatinine >6 × the ULN | Permanently discontinue |
| Rash | Grade 3 | Withhold dose[a] |
| | Grade 4 | Permanently discontinue |
| Encephalitis | New-onset moderate or severe neurologic signs or symptoms | Withhold dose[a] |
| | Immune-mediated encephalitis | Permanently discontinue |
| Other | Other Grade 3 adverse reaction<br>First occurrence<br>Recurrence of same Grade 3 adverse reactions | <br>Withhold dose[a]<br>Permanently discontinue |
| | Life-threatening or Grade 4 adverse reaction | Permanently discontinue |
| | Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks | Permanently discontinue |
| | Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer | Permanently discontinue |

*Toxicity was graded per NCI CTCAE v. 4.03.

[a] Resume treatment when adverse reaction returns to Grade 0 or 1.

## 6.1 Management of Nivolumab-Related Adverse Events

Management algorithms for the following nivolumab-related AEs are located in Appendix G – gastrointestinal, renal, pulmonary, hepatic, endocrinopathy, skin, and neurological.

### 6.1.1 Management of Infusion-Related Reactions

Nivolumab can cause severe infusion reactions, which have been reported in less than 1% of patients in clinical trials. Discontinue nivolumab in patients with Grade 3 or 4 infusion

reactions. Interrupt or slow the rate of infusion in patients with Grade 1 or 2 infusion reactions. For management of infusion-related side effects, refer to institutional guidelines.

# 7. STUDY ASSESSMENTS AND EVALUATIONS

## 7.1 Overview

All patients should visit the study center on the days specified within this protocol. The complete Schedule of Assessments for this study is shown in Appendix E. The baseline physical examination, medical history, ECOG PS, complete blood count (CBC) with differential and platelets, comprehensive metabolic profile (CMP), and prothrombin time (PT)/partial thromboplastin time (PTT)/International Normalized Ratio (INR) should be done ≤7 days prior to initiation of treatment. A pregnancy test must be performed within 72 hours of Cycle 1 Day 1. PET-CT scans should be performed ≤6 weeks prior to initiation of treatment. ECG and research samples should be performed ≤28 days prior to initiation of study treatment.

## 7.2 Baseline Study Assessments

The following information will be collected and procedures will be performed for each patient at screening:

- Written informed consent prior to any other study-related procedures (≤28 days prior to initiation of treatment)
- Medical history
    - Prior systemic therapy and radiotherapy for HL
    - Results of pre-transplant PET-CT (if done)
- Physical examination, measurements of height (first visit), weight, and vital signs (resting heart rate, BP, respiratory rate, and oral temperature)
- ECOG performance status (see Appendix A)
- 12-lead ECG
- Concomitant medication review
- CBC with 3-part differential and platelets
- CMP to include: glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, calcium, carbon dioxide ($CO_2$), alkaline phosphatase (ALP), AST, ALT, total bilirubin, total protein, and albumin
- Coagulation analysis: PT/INR/PTT
- Serum or urine pregnancy test (must be performed within 72 hours of Cycle 1 Day 1)
- PET-CT scans ≤6 weeks prior to initiation of study treatment

- Bone marrow biopsy, only if there is prior evidence of bone marrow involvement. If bone marrow biopsy needs to be repeated, it should be done ≤28 days prior to initiation of study treatment.

## 7.3 Study Treatment Assessments

### 7.3.1 Day 1 of Each Cycle (±2 days as long as interval between doses is 12-16 days)

- Physical examination, including measurement of weight and vital signs
- ECOG performance status
- AE assessment
- Concomitant medication review
- CBC, including 3-part differential and platelets
- CMP
- Pre-dose research blood sample for correlative analysis (**Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 3 Day 1 only**)

## 7.4 End of Study Treatment

After withdrawal from or completion of protocol treatment, patients must be followed for AEs for 100 calendar days after the last dose of study drug. The following assessments will be performed:

- Physical examination, including measurement of weight and vital signs
- ECOG performance status
- AE assessment
- Concomitant medication review
- CBC, including 3-part differential and platelets
- CMP
- Serum or urine pregnancy test
- Research blood sample for correlative analysis

## 7.5 Response Assessment

Patients should have PET-CT scans done per institution standard of care. PET-CT scans are required 1-3 months post-ASCT prior to initiation of therapy, 6 months post-ASCT, and 1 year post-ASCT. If there is prior evidence of bone marrow involvement, patients should also have bone marrow biopsy performed if in CR at these staging visits to document response.

Patients discontinuing therapy early receiving >6 cycles with measurable disease at baseline are recommended to have an EOT PET-CT. Patients ending treatment early need to have a PET-CT at 1 year post-ASCT unless patient progresses or starts a new therapy.

### 7.6 Follow-up

Patients will be followed every month (±1 week) for 3 months and then every 3 months thereafter from the date of last dose of nivolumab for up to 2 years. A research blood sample will be taken 1 year after the first dose of nivolumab. A phone call may be used to assess survival and to record initiation of an alternative form of treatment for lymphoma after response assessment at 1 year post-ASCT.

## 8. DRUG FORMULATION, AVAILABILITY, ADMINISTRATION, AND TOXICITY INFORMATION

### 8.1 Nivolumab

| Investigational Product | Dosage Form and Strength | Manufacturer |
|---|---|---|
| Nivolumab | 100 mg/10 mL (10 mg/mL) | Bristol-Myers Squibb |

#### 8.1.1 Labeling, Packaging, Supply, and Storage

Nivolumab will be supplied in 10-cc type I flint glass vials with butyl rubber stoppers and sealed with aluminum seals by Bristol-Myers Squibb.

Store under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light by storing in the original package until time of use. Do not freeze or shake.

All study drugs must be kept in a secure place under appropriate storage conditions. Storage conditions for nivolumab are included on the investigational product label.

Sarah Cannon Development Innovations must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

#### 8.1.2 Preparation and Administration of Nivolumab

Nivolumab is administered as an IV infusion over 60 minutes.

Preparation and administration instructions will be provided in the nivolumab Investigator's Brochure (IB).

#### 8.1.3 Precautions and Risks Associated with Nivolumab

Precautions and risks are located in the nivolumab IB. Management of nivolumab-related AEs is provided in Appendix G.

### 8.2 Accountability for All Study Drugs

The Principal Investigator (PI, or designee) is responsible for accountability of all used and unused study drug supplies at the site.

All study drug inventories must be made available for inspection by the Sponsor or its representatives and regulatory agency inspectors upon request.

At the end of the study, all Sarah Cannon Development Innovations Drug Accountability Record Form(s) will be completed by the site and sent to the Sarah Cannon Development Innovations Regulatory Department. Study drug supplies must not be destroyed unless prior approval has been granted by the Sponsor or its representative. Please contact Sarah Cannon Development Innovations regarding disposal of any study drug.

## 9. RESPONSE EVALUATIONS AND MEASUREMENTS

Lymphoma progression will be assessed using the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (Cheson et al. 2014, see Appendix F). Progression will be assessed 6 months post-ASCT and 1 year post-ASCT.

## 10. STATISTICAL CONSIDERATIONS

### 10.1 Statistical Design

This is a multicenter, open-label, Phase II study of nivolumab as maintenance therapy after ASCT in patients with HL at risk of relapse or progression. The primary, secondary and exploratory objectives and endpoints are found in Section 2.

### 10.2 Sample Size Considerations

The null hypothesis to be tested is that the true 12-month PFS is 50% against a two-sided alternative hypothesis of a 70% PFS rate. The 50% 6-month PFS rate was obtained from the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (Cheson et al. 2014, see Appendix F). A two-sided, one-sample log-rank test calculated from a sample of 36 evaluable subjects achieves 80.3% power at a 0.050 significance level to detect an improvement of 20% in 12-month PFS.

The probability that a subject experiences an event during the study is 0.4579. The expected number of events during the study is 16. It is assumed that the survival time distributions of both groups are approximated reasonably well by the Weibull distribution with a shape parameter of 1.00. These proportions assume an enrollment period of 18 months and a follow-up period of 12 months after the last subject is added. In order to allow for a 10% dropout rate, a total of 40 patients will be enrolled. The sample size was calculated using PASS version 14.

### 10.3 Analysis Population

The following analysis populations will be used:

- Full Analysis Set (FAS) is defined as all subjects who have received at least one dose of study medication.

- Efficacy-Evaluable Population (EFF) is defined as all subjects receiving at least two cycles of study medication.
- Safety Population (SAF) is defined as all patients who have received at least one dose of study treatment. This population will be used for the safety analysis.

## 10.4 Data Analysis

Descriptive statistics, including mean, median, standard deviations and ranges for all continuous measures will be tabulated and reported. Percentages and frequencies for all categorical measures will also be presented. Time-to-events endpoints will be reported using Kaplan-Meier estimates, with 95% a CI for median time to event.

### 10.4.1 Demographics and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized. Data to be tabulated will include demographic features such as age, sex and race, as well as disease-specific characteristics.

The number and percentages of patients screened, randomized, treated, completed the treatment/study and withdrawn from treatment/study for any reasons will be presented.

### 10.4.2 Efficacy Analysis

The primary efficacy analysis will be performed using the FAS. Sensitivity analyses will be performed using the Efficacy-Evaluable Population (EFF).

- Progression-Free Survival (PFS), defined as the time from the first day of study drug administration (Day 1) to disease progression as defined by the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (Cheson et al. 2014, see Appendix F), or death on study. Patients who are alive and free from disease progression will be censored at the date of last tumor assessment.

For PFS Kaplan-Meier curves will be generated and the median time to event and the associated 95% CI be provided. Kaplan-Meier estimates will also be produced for the following specified time points: 12 months and 24 months. The hazard ratio and the 95% CI for these endpoints between the two treatment groups will be calculated.

### 10.4.3 Safety Analysis

Safety will be assessed through the analysis of the reported incidence of treatment-emergent AEs. Treatment-emergent AEs are those with an onset on or after the initiation of therapy, and will be graded according to NCI CTCAE v 4.03. A copy of CTCAE scoring system may be downloaded from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

The AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA), and summarized using system organ class and preferred term for all patients in the Safety Population. In addition, summaries of serious adverse events (SAEs), AEs leading to treatment

discontinuation, AEs by maximum NCI CTCAE grade, and AEs related to study treatment will also be presented.

Other safety endpoints including laboratory results and vital signs will be summarized for all patients in the Safety Population.

Concomitant medications will be listed and summarized and coded using the World Health Organization-Drug Dictionary.

### 10.4.4 Exploratory Analysis

The scope and details of the exploratory analysis, including correlative biomarker analysis, will be detailed in the Statistical Analysis Plan (SAP).

## 10.5 Analysis Time Points

### 10.5.1 Final Analysis

The final analysis of the study will occur when all enrolled subjects have received at least 2 cycles of nivolumab and have completed 12 month post-ASCT disease assessment.

### 10.5.2 Planned Interim Analysis

There is no planned interim analysis for this study.

# 11. SAFETY REPORTING AND ANALYSES

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs, measurement of protocol-specified hematology, clinical chemistry, and other protocol-specified tests in the eCRFs that are deemed critical to the safety evaluation of the study drug.

The PI is responsible for recognizing and reporting AEs to the Sarah Cannon Development Innovations Safety Department (see Section 11.2). It is the Sponsor's responsibility to report relevant SAEs to the applicable local, national, or international regulatory bodies. In addition, Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of that IRB.

The PI is also responsible for ensuring that every staff member involved in the study is familiar with the content of this section.

## 11.1 Definitions

### 11.1.1 Adverse Events

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgment about causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, dose or including overdose.

### 11.1.2 Serious Adverse Event

**An AE or a suspected adverse reaction (SAR) is considered "serious" if it results in any of the following outcomes:**

- **Death**
- **A life-threatening AE**
- **Inpatient hospitalization of at least 24-hours or prolongation of existing hospitalization**
- **A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**
- **A congenital anomaly/birth defect**

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

It is important to distinguish between "serious" and "severe" AE, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. Seriousness serves as the guide for defining regulatory reporting obligations. "Serious" is a regulatory definition and is based on patient/event outcome or action usually associated with events that pose a threat to a patient's life or vital functions. For example, nausea which persists for several hours may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs on the eCRF and SAEs on the SAE Report Form.

### 11.1.3 Adverse Reaction

An adverse reaction means any AE caused by a drug. Adverse reactions are a subset of all SARs where there is a reason to conclude that the drug caused the event.

### 11.1.4 Suspected Adverse Reaction

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE. An SAR implies a lesser degree of certainty about causality than AE, which means any AE caused by a drug.

### 11.1.5 Recording and Reporting of Adverse Events

**Recording of Adverse Events**

All AEs from any patient that occur during the course of the research study will be recorded in the eCRF, and the Investigator will give his or her opinion as to the relationship of the AE to the study drug treatment (i.e., whether the event is related or unrelated to study drug administration).

All AEs should be documented. A description of the event, including its date of onset and resolution, whether it constitutes a SAE or not, any action taken (e.g., changes to study treatment), and outcome, should be provided, along with the Investigator's assessment of causality (i.e., the relationship to the study treatment[s]). For an AE to be a suspected treatment-related event there should be at least a reasonable possibility of a causal relationship between the protocol treatment and the AE. Adverse events will be graded according to the NCI CTCAE v4.03, and changes will be documented.

If the AE is serious, it should be reported immediately to the Sarah Cannon Development Innovations Safety Department. Other untoward events occurring in the framework of a clinical study are to be recorded as AEs (i.e., AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

Any clinically significant signs and symptoms; abnormal test findings; changes in physical examination; hypersensitivity; and other measurements that occur will be reported as an AE, and collected on the relevant eCRF screen.

Test findings will be reported as an AE if: the test result requires an adjustment in the study drug(s) or discontinuation of treatment, and/ or test findings require additional testing or surgical intervention, a test result or finding is associated with accompanying symptoms, or a test result is considered to be an AE by the Investigator.

**Reporting Period for Adverse Events**

All AEs, regardless of seriousness or relationship to nivolumab treatment (called study treatment), spanning from the start of study treatment until 100 calendar days after discontinuation or completion of study treatment as defined by the clinical study for that patient, are to be recorded on the corresponding screen(s) included in the eCRF.

All AEs resulting in discontinuation from the study should be followed until resolution or stabilization. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the Investigator, the AE or laboratory abnormality/ies are not likely to improve because of the underlying disease. In this case, the Investigators must record his or her reasoning for this decision in the patient's medical record.

After 100 days following the completion of protocol-specific treatment or discontinuation, only AEs, SAEs, or deaths assessed by the Investigator as treatment-related are to be reported.

### 11.1.6 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, Investigators should apply the following general guideline:

> **YES:** There is a plausible temporal relationship between the onset of the AE and administration of the study medication, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies, and/or the AE follows a known pattern of response to the study drug, and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
>
> **NO:** Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication), and/or the AE has no plausible temporal relationship to study drug administration (e.g., cancer diagnosed 2 days after first dose of study drug).

## 11.2 Serious Adverse Event Reporting by Investigators

Adverse events classified by the treating Investigator as serious require expeditious handling and reporting to the Sarah Cannon Development Innovations Safety Department in order to comply with regulatory requirements. Determination of life-threatening or serious is based on the opinion of either the Sponsor or the Investigator.

Serious AEs may occur at any time from the start of study treatment through 100 days after the last study treatment. **The Sarah Cannon Development Innovations Safety Department must be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel.**

To report a SAE, the SAE Report Form should be completed with the necessary information.

The SAE report should be sent to the Sarah Cannon Development Innovations Safety Department via fax or email using the using the following contact information (during both business and non-business hours):

Sarah Cannon Development Innovations Safety Department

Safety Dept. Fax #: 1-866-807-4325

Safety Dept. Email: CANN.SAE@SCRI-Innovations.com

Transmission of the SAE report should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the Sarah Cannon Development Innovations Safety Department as soon as it is available; these reports should be submitted using the Sarah Cannon Development Innovations

SAE Report Form. The detailed SAE reporting process will be provided to the sites in the SAE reporting guidelines contained in the study reference manual.

Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of the responsible IRB.

## 11.3 Recording of Adverse Events and Serious Adverse Events

### 11.3.1 Diagnosis versus Signs and Symptoms

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the PI or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or AE eCRF screen). If a diagnosis is subsequently established, it should be reported as follow-up information becomes available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per Lugano Classification [Cheson et al. 2014, see Appendix F]), should not be reported as an SAE.

### 11.3.2 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the AE eCRF screen. If a persistent AE becomes more severe or lessens in severity, it should be recorded on a separate SAE Report Form and/or AE eCRF screen.

A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or AE eCRF screen.

### 11.3.3 Abnormal Laboratory Values

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE or SAE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant eCRF screen. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE eCRF screen.

Abnormal laboratory values will be reported as an AE if: the laboratory result requires an adjustment in the study drug(s) or discontinuation of treatment, and/ or laboratory findings require additional testing or surgical intervention, a laboratory result or finding is associated with accompanying symptoms, or a laboratory result is considered to be an AE by the Investigator.

### 11.3.4 Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the Investigator solely to progression of disease will be recorded on the "Study Discontinuation" eCRF screen. All other on study deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the Sarah Cannon Development Innovations Safety Department.

When recording a SAE with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE Report Form and Adverse Event screen of the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" (Not Otherwise Specified) on the eCRF Adverse Event screen. During post-study survival follow-up, deaths attributed to progression of disease will be recorded only on the "After Progressive Disease Follow-Up" eCRF screen.

### 11.3.5 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization of >24 hours or prolongation of pre-existing hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalizations that do not require reporting as an SAE.

Treatment within or admission to the following facilities is not considered to meet the criteria of "inpatient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency department or emergency room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, custodial care or respite care facility

Hospitalization during the study for a pre-planned surgical or medical procedure (one which was planned prior to entry in the study) does not require reporting as an SAE to the Sarah Cannon Development Innovations Safety Department.

### 11.3.6 Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be recorded on the General Medical History eCRF screen. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an SAE Report Form and/or AE eCRF screen, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

### 11.3.7 New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the seriousness criteria (see Section 11.1.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

### 11.3.8 Pregnancy, Abortion, and Birth Defects/Congenital Anomalies

If a patient becomes pregnant while enrolled in the study, a Pregnancy Form (a paper report form, not available within the eCRF) should be completed and faxed to the Sarah Cannon Development Innovations Safety Department. The Sarah Cannon Development Innovations Safety Department should be notified expeditiously, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to Sarah Cannon Development Innovations Safety Department.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to the Sarah Cannon Development Innovations Safety Department immediately. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Congenital anomalies/birth defects always meet SAE criteria and should therefore be expeditiously reported as an SAE using the previously described process for SAE reporting. A Pregnancy Form should also have been previously completed, and will need to be updated to reflect the outcome of the pregnancy.

### 11.3.9 Nivolumab Overdose

Symptomatic and non-symptomatic overdose must be reported in the eCRF. Any accidental or intentional overdose with the study treatment that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the Sarah Cannon Development Innovations Safety Department no greater than 24 hours from first knowledge of the event using the corresponding screens in the eCRF and following the same process described for SAE reporting (see Section 11.2) if the overdose is symptomatic.

For information on how to manage an overdose of nivolumab, see the IB.

## 11.4 Sponsor Serious Adverse Event Reporting Requirements

Sarah Cannon Development Innovations Safety Department will forward SAE information to BMS Global Pharmacovigilance at Worldwide.Safety@bms.com within 1 business day of Sarah Cannon Development Innovations Safety Department personnel becoming aware of the SAE.

Sarah Cannon Development Innovations is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating Investigators, in accordance with International Council for Harmonisation (ICH) guidelines and FDA regulations.

### 11.4.1 Sponsor Assessment of Unexpected

The Sponsor is responsible for assessing an AE or suspected AE as "unexpected."

An AE or SAR is considered "unexpected" when the following conditions occur:

- Event(s) is not mentioned in the IB (or current US Package Insert [USPI])
- Event(s) is not listed at the specificity or severity that has been observed
- An event(s) is not consistent with the General Investigative Plan or in the current application
- Includes AEs or SAR that may be anticipated from the pharmacological properties of the study drug, or that occur with members of the drug class, but that have previously been observed under investigation

When applicable, an unexpected AE may also apply to an event that is not listed in the current USPI or an event that may be mentioned in the USPI, but differs from the event because of greater severity or specificity.

Known as Suspected Unexpected Serious Adverse Reactions (SUSAR), these events suspected (by the Investigator or Sponsor) to be related to the study drug, are unexpected (not listed in the IB), are serious (as defined by the protocol) and require expedient submission to relevant health authorities within 7 days (fatal or life-threatening event) or 15 days (all serious events), or as defined by law. The term SUSAR is used primarily in the reporting of events to regulatory authorities.

Expected AEs are those events that are listed or characterized in the Package Insert or current IB.

### 11.4.2 Sponsor Reporting for Clinical Studies Under an Investigational New Drug Application

All written investigational new drug (IND) Safety Reports submitted to the FDA by the Sarah Cannon Development Innovations Safety Department must also be faxed to pharmaceutical company(ies) that are supporting the study with either funding or drug supply:

BMS Global Pharmacovigilance

BMS Safety SAE Fax #: 609-818-3804

Worldwide.Safety@bms.com

## 12. QUALITY ASSURANCE AND QUALITY CONTROL

### 12.1 Study Monitoring, Auditing, and Inspecting

The Investigator will permit study-related monitoring, quality audits, and inspections by the Sponsor or its representative(s), government regulatory authorities, and the IRB/EC of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The Investigator will ensure the capability for inspections of

applicable study-related facilities. The Investigator will ensure that the study monitor or any other compliance or Quality Assurance reviewer is given access to all study-related documents and study-related facilities.

At the Sponsor's discretion, Source Document Verification (SDV) may be performed on all data items or a percentage thereof.

Participation as an Investigator in this study implies the acceptance of potential inspection by government regulatory authorities, the Sponsor or its representative(s).

## 13. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This research study will be conducted according to the standards of Good Clinical Practice (GCP) outlined in the ICH E6 Tripartite Guideline and CFR Title 21 part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s).

### 13.1 Institutional Review Board Approval

The clinical study protocol, informed consent form (ICF), IB, available safety information, patient documents (e.g., study diary), patient recruitment procedures (e.g., advertisements), information about payments (i.e., PI payments) and compensation available to the patients and documentation evidencing the PI's qualifications should be submitted to the IRB for ethical review and approval if required by local regulations, prior to the study start.

The PI/Sponsor and/or designee will follow all necessary regulations to ensure appropriate, initial, and on-going, IRB study review. The PI/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by the Sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

Safety updates for nivolumab will be prepared by the Sponsor or its representative as required, for distribution to the Investigator(s) and submission to the relevant IRB.

### 13.2 Regulatory Approval

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation. If required, the Sponsor will also ensure that the implementation of substantial amendments to the protocol and other relevant study documents happen only after approval by the relevant regulatory authorities.

### 13.3 Informed Consent

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular study after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated ICF.

The ICF will be submitted for approval to the IRB that is responsible for review and approval of the study. Each consent form must include all of the relevant elements currently required by the FDA, as well as local county authority or state regulations and national requirements.

Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the research study. Once the essential information has been provided to the prospective candidate, and the Investigator is sure that the individual candidate understands the implications of participating in this research study, the candidate will be asked to give consent to participate in the study by signing an ICF. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the ICF, to include the patient's signature, will be provided by the Investigator to the patient.

If an amendment to the protocol substantially alters the study design or the potential risks to the patients, the patient's consent to continue participation in the study should be obtained.

### 13.3.1 Confidentiality

#### 13.3.1.1 Patient Confidentiality

Confidentiality of patient's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require that, in order to participate in the study, a patient must sign an authorization form for the study that he or she has been informed of following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- That health information may be further disclosed by the recipients of the information and that if the information is disclosed the information may no longer be protected by federal or state privacy laws
- The information collected about the research study will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the study
- Whether the authorization contains an expiration date
- The rights of a research patient to revoke his or her authorization

In the event that a patient revokes authorization to collect or use his or her PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled study period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the Investigator and institution permit authorized representatives of the Sponsor, the regulatory

authorities and the IRB direct access to review the patient's original medical records at the site for verification of study-related procedures and data.

Measures to protect confidentiality include: only a unique study number will identify patients in the eCRF or other documents submitted to the Sponsor. This information, together with the patient's date of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the eCRF. No material bearing a patient's name will be kept on file by Sponsor. Patients will be informed of their rights within the ICF.

#### 13.3.1.2 Investigator and Staff Information

Personal data of the Investigators and sub-Investigators may be included in the Sarah Cannon Development Innovations database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the Investigator or sub-Investigator, Sarah Cannon Development Innovations shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

### 13.4 Financial Information

The finances for this clinical study will be subject to a separate written agreement between the Sarah Cannon Development Innovations, LLC and applicable parties. Any Investigator financial disclosures as applicable to 21CFR Part 54 shall be appropriately provided.

## 14. RESEARCH RETENTION AND DOCUMENTATION OF THE STUDY

### 14.1 Amendments to the Protocol

Amendments to the protocol shall be planned, documented, and signature-authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor or its representatives. All amendments require review and approval of all pharmaceutical companies and the PI supporting the study. The written amendment must be reviewed and approved by the Sponsor, and submitted to the IRB at the Investigator's facility for the board's approval.

Amendments specifically involving change to study design, risk to patient, increase to dosing or exposure, patient number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the IRB of record for the Investigator's facility.

The amendment will be submitted formally to the FDA or other regulatory authorities by the Sponsor as applicable, and IRB approval obtained, and specifically when an increase to dosing or patient exposure and/or patient number has been proposed; or, when the addition or removal of an Investigator is necessitated.

Items requiring a protocol amendment approval from IRB and/or FDA or other regulatory authorities includes, but are not limited to, the following:

- Change to study design

- Risk to patient
- Increase to dose or patient exposure to drug
- Patient number increase
- Addition or removal of tests and / or procedures
- Addition/removal of a new Investigator

It should be further noted that, if an amendment to the protocol substantially alters the study design or the potential risks to the patients, their consent to continue participation in the study should be obtained.

## 14.2 Documentation Required to Initiate the Study

Before the study may begin certain documentation required by FDA regulations and ICH GCP must be provided by the Investigator. The required documentation should be submitted to:

Sarah Cannon Development Innovations
Regulatory Department
1100 Dr. Martin L. King Jr. Blvd., Suite 800
Nashville, TN 37203

Documents at a minimum required to begin a study in the US include, but are not limited to, the following:

- A signature-authorized protocol and contract
- A copy of the official IRB approval of the study and the IRB members list
- Current Curricula Vitae for the PI and any sub-Investigator(s) who will be involved in the study
- Indication of appropriate accreditation for any laboratories to be used in the study and a copy of the normal ranges for tests to be performed by that laboratory
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed
- A copy of the IRB-approved consent form (and patient information sheet, if applicable) containing permission for audit by representatives of Sarah Cannon Development Innovations, the IRB, and the FDA and other regulatory agencies (as applicable)
- Financial disclosure forms for all Investigators listed on Form FDA 1572 (if applicable)
- Site qualification reports, where applicable
- Verification of PI acceptability from local and/or national debarment list(s)

## 14.3 Study Documentation and Storage

The PI must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the eCRFs are to be included on this document. All entries in the patient's eCRF are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations, and activities from which the patient's eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The PI and each study staff member is responsible for maintaining a comprehensive and centralized filing system (e.g., regulatory binder or Investigator study file [ISF]) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, protocol and any amendments, signed ICFs, copies of completed eCRFs, IRB approval documents, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain PI name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the eCRF must be maintained and be readily available.

The Sponsor shall maintain adequate investigational product records and financial interest records as per 21CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by the FDA; or, in the event that the marketing application has not been approved by the FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and the FDA has been notified of the discontinuation.

The IRB shall maintain adequate documentation / records of IRB activities as per 21CFR Part 56.115 for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories, and any other study-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by the FDA; or, in the event that the marketing application has not been approved by the FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and the FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the Investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records e.g., eCRFs, medical records), all original, signed ICFs, and copies of all eCRFs, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). Sponsor will notify the Investigator(s)/institutions(s) when the study-related records are no longer required.

If the Investigator relocates, retires, or for any reason withdraws from the study, both the Sponsor and its representative should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor. The Investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met. All study files will be maintained by the Sponsor (Sarah Cannon Development Innovations) throughout the study, and will be held by the Sponsor at the conclusion of the study.

### 14.4 Data Collection

The study eCRF is the primary data collection instrument for the study. Case report forms will be completed using the English language and should be kept current to enable the Sponsor to review the patients' status throughout the course of the study.

In order to maintain confidentiality, only study number, patient number, and year of birth will identify the patient in the eCRF. If the patient's name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to Sarah Cannon Development Innovations and replaced instead with the patient number and patient's initials. The Investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

All data requested in the eCRF must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the field was "Not Done" or "Unknown." For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The Investigator will electronically sign and date the patient eCRF casebook indicating that the data in the eCRF has been assessed. Each completed eCRF will be signed and dated by the PI, once all data for that patient is final.

### 14.5 Disclosure and Publication Policy

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Sponsor reserves the right

to release literature publications based on the results of the study. Results from the study will be published/presented as per the Sponsor's publication process.

Inclusion of the Investigator in the authorship of any multicenter publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the study. The Investigator acknowledges that the study is part of a multicenter study and agrees that any publication by the Investigator of the results of the study conducted at research site shall not be made before the first multicenter publication. In the event there is no multicenter publication within fifteen (15) months after the study has been completed or terminated at all study sites, and all data has been received, the Investigator shall have the right to publish its results from the study, subject to the notice requirements described herein and subject to acknowledgement of the Sponsor as appropriate. Investigator shall provide the Sponsor thirty (30) days to review a manuscript or any poster presentation, abstract or other written or oral material which describes the results of the study for the purpose only of determining if any confidential or patentable information is disclosed thereby. If the Sponsor requests in writing, the Investigator shall withhold any publication or presentation an additional sixty (60) days solely to permit the Sponsor to seek patent protection and to remove any Sarah Cannon Development Innovations Confidential Information from all publications.

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## 16. APPENDICES

### Appendix A: ECOG Performance Status Criteria

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

## Appendix B: New York Heart Association (NYHA) Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease.

| Class | Functional Capacity | Objective Assessment |
|---|---|---|
| I | Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain. | No objective evidence of cardiovascular disease. |
| II | Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain. | Objective evidence of minimal cardiovascular disease. |
| III | Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain. | Objective evidence of moderately severe cardiovascular disease. |
| IV | Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased. | Objective evidence of severe cardiovascular disease. |

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

## Appendix C: Deauville 5-point scoring system

The **Deauville 5-point scoring system** is an internationally accepted and utilized five-point scoring system for the fluorodeoxyglucose (FDG) avidity of a Hodgkin's Lymphoma or non-Hodgkin Lymphoma tumor mass as seen on FDG PET:

- Score 1: No uptake above the background
- Score 2: Uptake ≤ mediastinum
- Score 3: Uptake > mediastinum but ≤ liver
- Score 4: Uptake moderately increased compared to the liver at any site
- Score 5: Uptake markedly increased compared to the liver at any site
- Score X: New areas of uptake unlikely to be related to lymphoma

## Barrington et al. 2010

Barrington SF, Qian W, Somer EJ, et al. Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma. Eur J Nucl Med Mol Imaging. 2010(10);37:1824–33.

## Appendix D: Guidelines for Female Patients of Childbearing Potential and Fertile Male Patients

**Acceptable Contraception Methods:**

Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 7 months after stopping treatment.

Highly effective contraception is defined as either:

**True Abstinence** When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

**Sterilization** When a woman of childbearing potential has had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to study entry. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.

**Male Partner Sterilization** When the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate.

**Use of a combination of any two of the following (one from a + one from b):**

a) Placement of an intrauterine device (IUD) or intrauterine system (IUS) or established use of oral, injected or implanted hormonal methods of contraception.

b) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

Fertile male patients, defined as all males physiologically capable of conceiving offspring, with female partners of childbearing potential must use condoms plus spermicidal agent during the study treatment period and for 7 months after the last dose of study drug, and should not father a child during this period.

Male patients must also refrain from donating sperm during their participation in the study and for 7 months after the last dose of study drug.

**The following are acceptable forms of barrier contraception:**

- Latex condom, diaphragm or cervical/vault cap when used with spermicidal foam/gel/film/cream/suppository

**Unacceptable Contraception Methods:** for women of childbearing potential include:

- IUD progesterone T

- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

**Pregnancies**

To ensure subject safety, each pregnancy in a subject on study treatment must be reported to the Sarah Cannon Development Innovations Safety Department within 24 hours of learning of its occurrence. The pregnancy should be followed up for 3 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the Investigator to **Sarah Cannon Development Innovations Safety Department**. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

**Women Not of Childbearing Potential are defined as Follows:**

- Women are considered postmenopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms).
- Women who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy).
- Women who are >45 years of age, not using hormone-replacement therapy and who have experienced total cessation of menses for at least 12 months OR who have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value <40 pg/mL (140 pmol/L).
- Women who are >45 years of age, using hormone-replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have had documented evidence of menopause based on FSH >40 mIU/mL and estradiol <40 pg/mL prior to initiation of hormone-replacement therapy.

## Appendix E: Schedule of Assessments for patients receiving study drug

| ASSESSMENTS | Baseline[a] | STUDY TREATMENT (*Cycles repeated every 2 weeks*) | | | |
|---|---|---|---|---|---|
| | | **Day 1 of every cycle (±2 days as long as interval between doses is 12-16 days)** | **Response assessed at 6 months and 1 year post-ASCT** | **End of Treatment[j]** | **Follow-Up[k]** |
| ***Tests and Observations*** | | | | | |
| Informed consent[a] | X | | | | |
| Medical history | X[b] | | | | |
| Physical exam[c] | X[b] | X | | X | |
| Vital Signs[d] | X[b] | X | | X | |
| ECOG PS | X[b] | X | | X | |
| 12-lead ECG | X[b] | | | | |
| Adverse event evaluation | | X | | X | X[j] |
| Concomitant medication review | X[b] | X | | X | |
| ***Study Treatment*** | | | | | |
| Nivolumab | | X | | | |
| ***Laboratory Observations[m]*** | | | | | |
| CBC, 3-part differential, and platelets | X[b] | X | | X | |
| CMP[e] | X[b] | X | | X | |
| PT/PTT/INR[f] | X[b] | | | | |
| Serum or Urine Pregnancy Test[g] | X[b] | | | X[g] | |
| Research blood sample[h] | | X (C1 D1, C2 D1, and C3 D1 only) | | X | X |
| ***Staging*** | | | | | |
| PET-CT scan | X[b] | | X[i] | | |
| Bone marrow biopsy[l] | X | | X | | |
| Survival | | | | | X |

## Appendix E: Schedule of Assessments (continued)

a Informed consent must be obtained ≤28 days prior to the initiation of treatment.

b The baseline physical examination, medical history, ECOG PS, complete blood counts (CBC) with differential and platelets, comprehensive metabolic profile (CMP), and PT/PTT/INR should be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of Cycle 1 Day 1 they do not have to be repeated. A pregnancy test must be performed within 72 hours of Cycle 1 Day 1. PET scans should be performed ≤6 weeks prior to initiation of treatment. ECG and research samples should be performed ≤28 days prior to initiation of study treatment.

c Physical examination will include measurements of height (pretreatment visit only), weight, and vital signs.

d Vital signs will include resting heart rate, blood pressure, respiratory rate, and temperature.

e CMP will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, $CO_2$, ALP, AST (SGOT), ALT (SGPT), total bilirubin, total protein, and albumin.

f If PT/PTT/INR are normal at baseline they do not need to be repeated. Patients requiring the initiation of an anti-coagulation therapy during study treatment should have coagulation tests performed according to standard practice guidelines.

g Serum or urine pregnancy tests are to be conducted in women of childbearing potential.

h A research blood sample will be taken at, pre-dose on Cycle 1 Day1, Cycle 2 Day 1, Cycle 3 Day 1, EOT (6 months), and 1 year after the first dose of nivolumab.

i Patients should have PET-CT scans done per institution standard of care. PET-CT scans are required post-ASCT prior to initiation of therapy, 6 months post-ASCT, and 1 year post-ASCT. Patients discontinuing therapy early receiving >6 cycles with measurable disease at baseline are recommended to have an EOT PET-CT. Patients ending treatment early need to have a PET-CT scan at 1 year post-ASCT unless patient progresses or starts a new therapy.

j EOT evaluations must be completed within 30 days after the last dose of study treatment. Patients must be followed for AEs for 100 calendar days after the last dose of nivolumab.

k Patients will be followed every month (±1 week) for 3 months and then every 3 months thereafter from the date of last dose of nivolumab for up to 2 years. A phone call may be used to assess survival and to record initiation of an alternative form of treatment for lymphoma after response assessment at 1 year post-ASCT.

l Bone marrow biopsy is requested at baseline only in patients with prior bone marrow involvement. At subsequent staging visits, patients with prior bone marrow involvement, if in CR, should also have bone marrow biopsy performed to document response.

m Laboratory samples from control patients will be collected as described in Section 5.4.2.

## Appendix F: Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification

These criteria are based upon the criteria from the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (Cheson et al. 2014)

| Revised Criteria for Response Assessment | | |
|---|---|---|
| Response and Site | PET-CT–Based Response | CT-Based Response |
| Complete | Complete metabolic response | Complete radiologic response (all of the following) |
| Lymph nodes and extralymphatic sites | Score 1, 2, or 3* with or without a residual mass on 5PS†<br>It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic | Target nodes/nodal masses must regress to ≤1.5 cm in LDi<br>No extralymphatic sites of disease |
| Nonmeasured lesion | Not applicable | Absent |
| Organ enlargement | Not applicable | Regress to normal |
| New lesions | None | None |
| Bone marrow | No evidence of FDG-avid disease in marrow | Normal by morphology; if indeterminate, IHC negative |
| Partial | Partial metabolic response | Partial remission (all of the following) |
| Lymph nodes and extralymphatic sites | Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size<br>At interim, these findings suggest responding disease<br>At end of treatment, these findings indicate residual disease | ≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites<br>When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value<br>When no longer visible, 0 x 0 mm<br>For a node >5 mm × 5 mm, but smaller than normal, use actual measurement for calculation |
| Nonmeasured lesions | Not applicable | Absent/normal, regressed, but no increase |
| Organ enlargement | Not applicable | Spleen must have regressed by >50% in length beyond normal |
| New lesions | None | None |
| Bone marrow | Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan | Not applicable |

| Revised Criteria for Response Assessment | | |
|---|---|---|
| Response and Site | PET-CT–Based Response | CT-Based Response |
| No response or stable disease | No metabolic response | Stable disease |
| Target nodes/nodal masses, extranodal lesions | Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment | < 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met |
| Nonmeasured lesions | Not applicable | No increase consistent with progression |
| Organ enlargement | Not applicable | No increase consistent with progression |
| New lesions | None | None |
| Bone marrow | No change from baseline | Not applicable |
| Progressive disease | Progressive metabolic disease | Progressive disease requires at least one of the following: |
| Individual target nodes/nodal masses | Score 4 or 5 with an increase in intensity of uptake from baseline and/or | PPD progression: |
| Extranodal lesions | New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment | An individual node/lesion must be abnormal with:<br>LDi >1.5 cm and<br>Increase by ≥50% from PPD nadir and<br>An increase in LDi or SDi from nadir<br>0.5 cm for lesions ≤2 cm<br>1.0 cm for lesions >2 cm<br>In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline<br>New or recurrent splenomegaly |
| Nonmeasured lesions | None | New or clear progression of pre-existing nonmeasured lesions |
| New lesions | New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered | Regrowth of previously resolved lesions A new node >1.5 cm in any axis<br>A new extranodal site <1.0 cm in any axis; if >1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma<br>Assessable disease of any size unequivocally attributable to lymphoma |
| Bone marrow | New or recurrent FDG-avid foci | New or recurrent involvement |

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

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

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

## Appendix G: Management Algorithms for Immuno-Oncology Agents

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

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

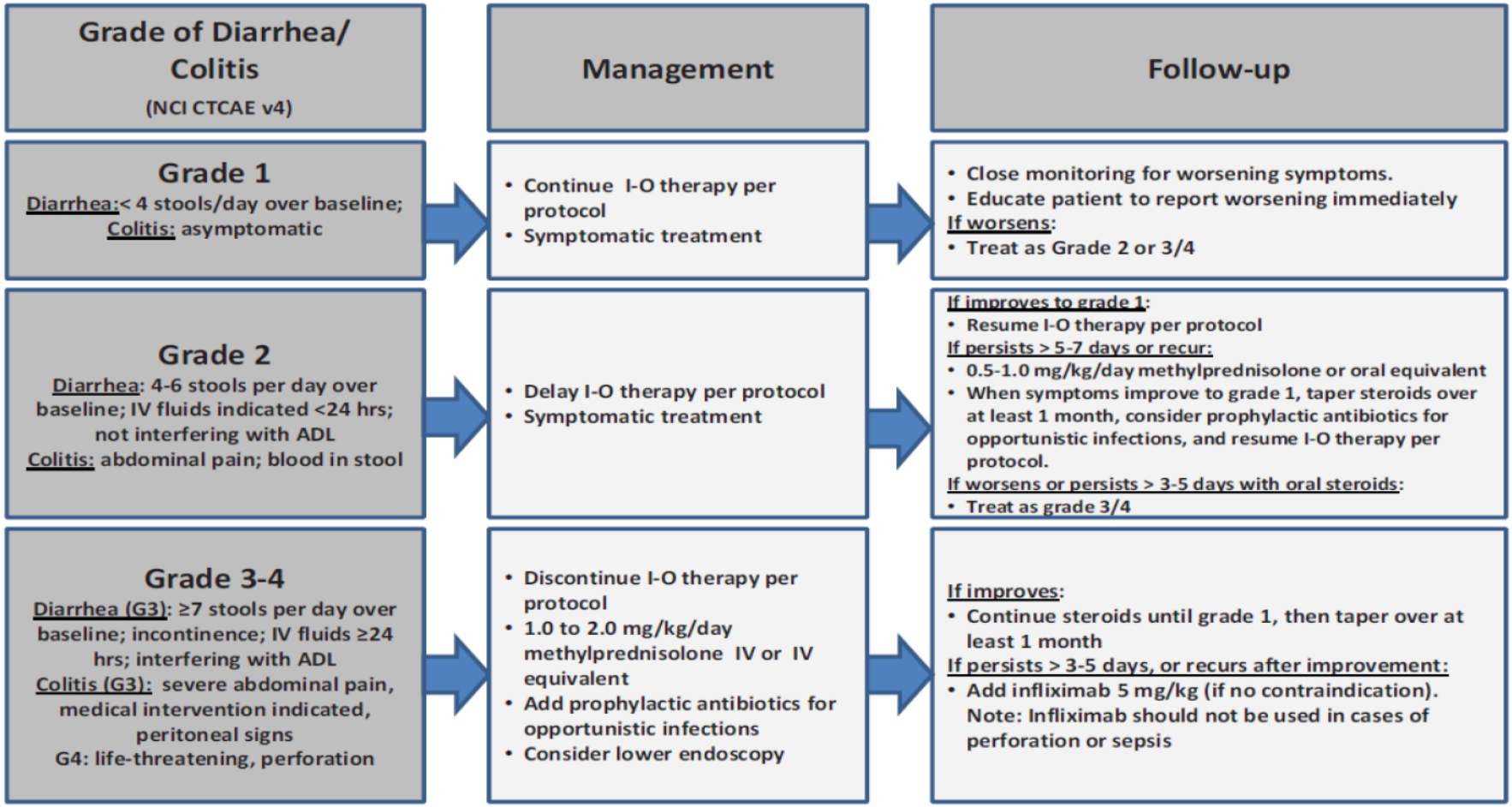
Corticosteroids are a primary therapy for immuno-oncology drug-related AEs. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent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

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

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

# GI Adverse Event Management Algorithm

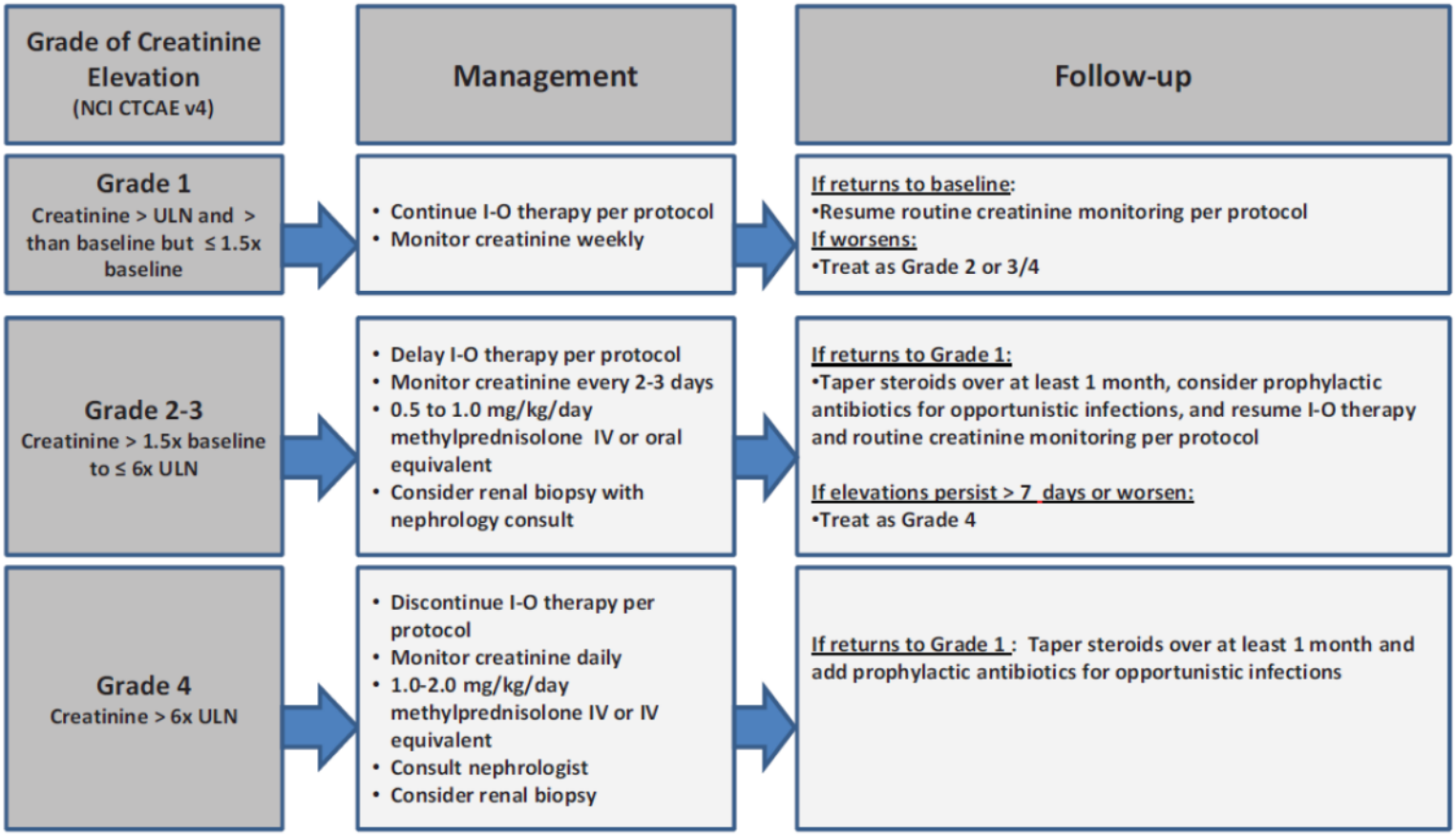
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.




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

# Renal Adverse Event Management Algorithm

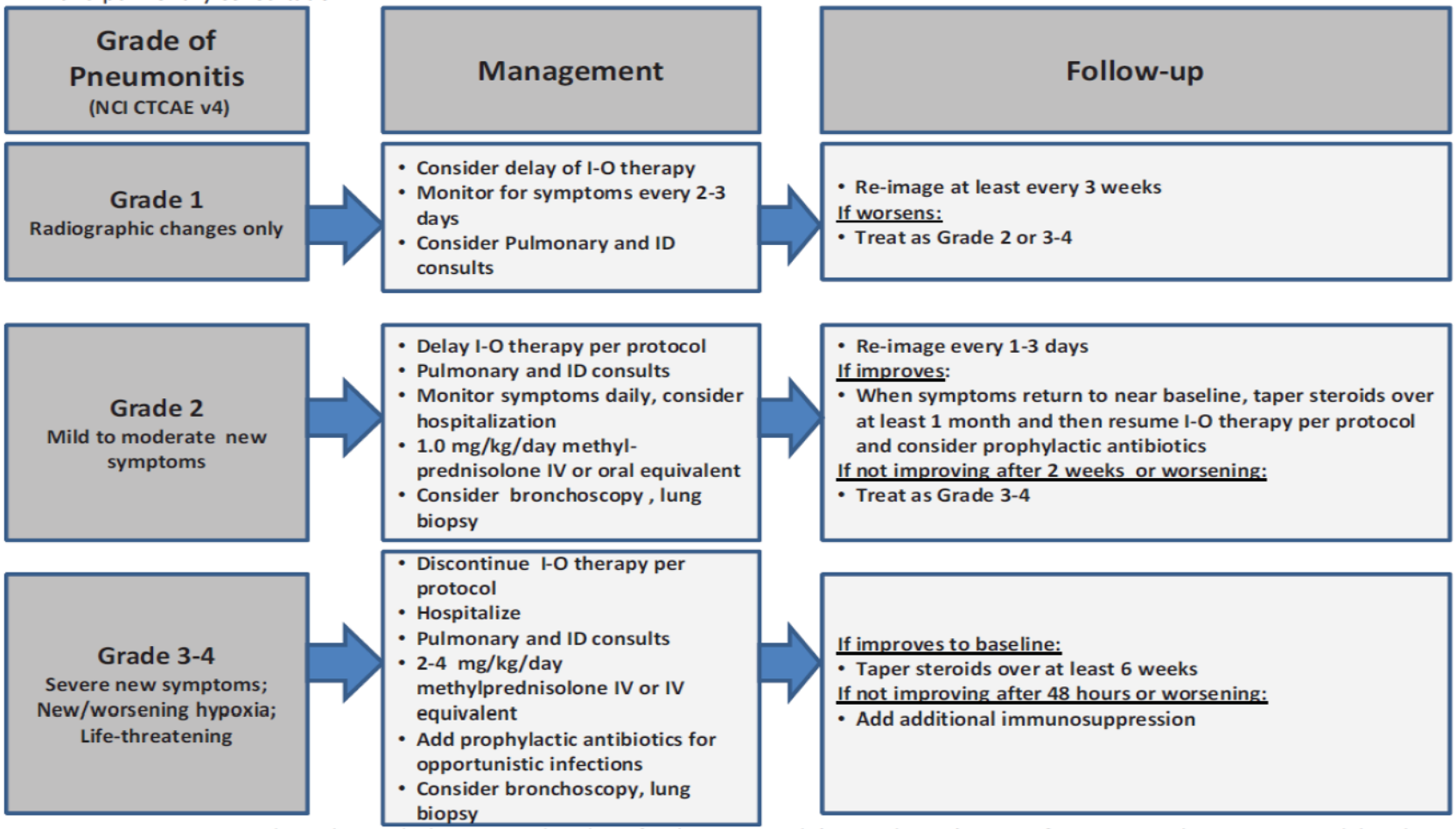
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy




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

# Pulmonary Adverse Event Management Algorithm

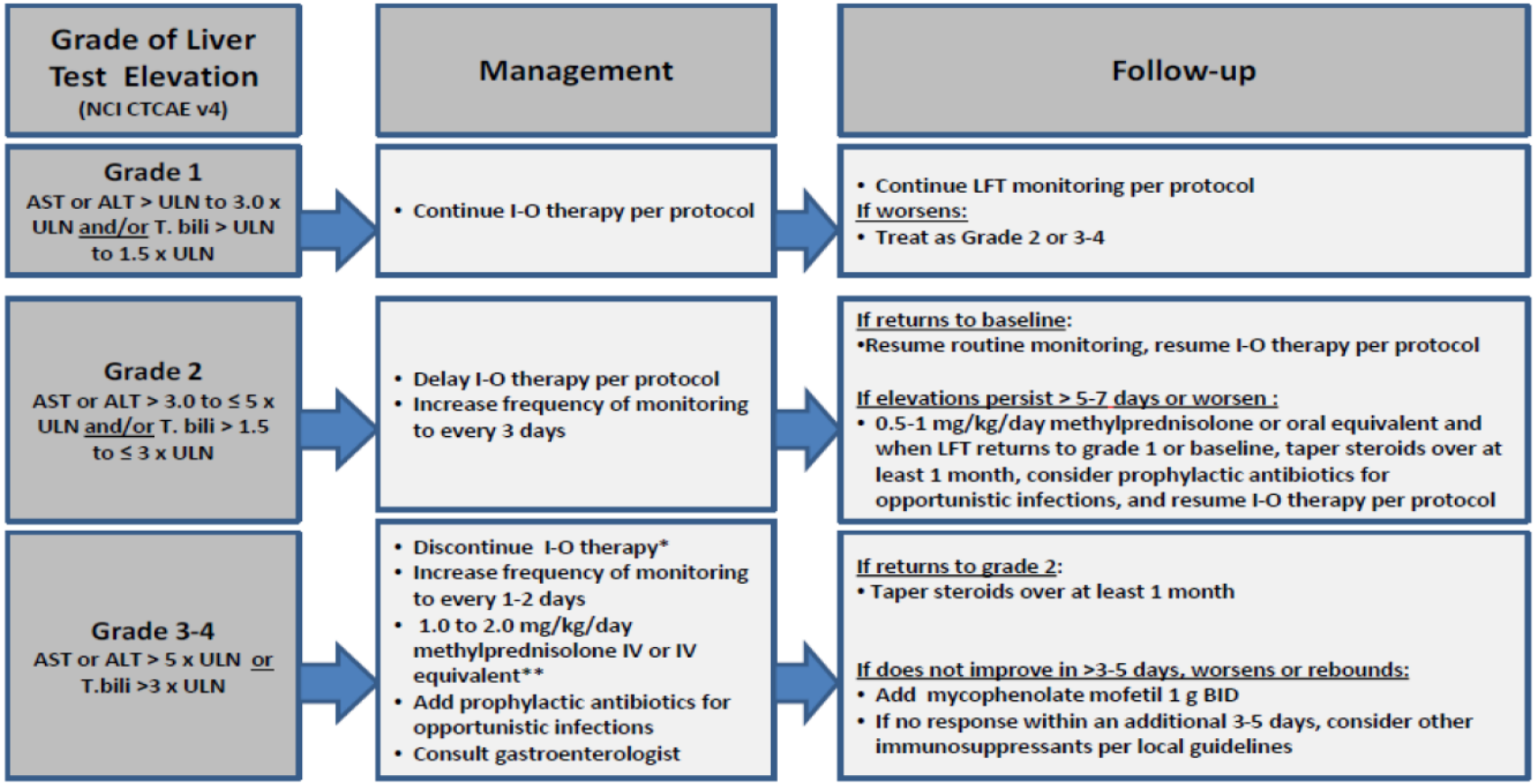
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.




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

# Hepatic Adverse Event Management Algorithm

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



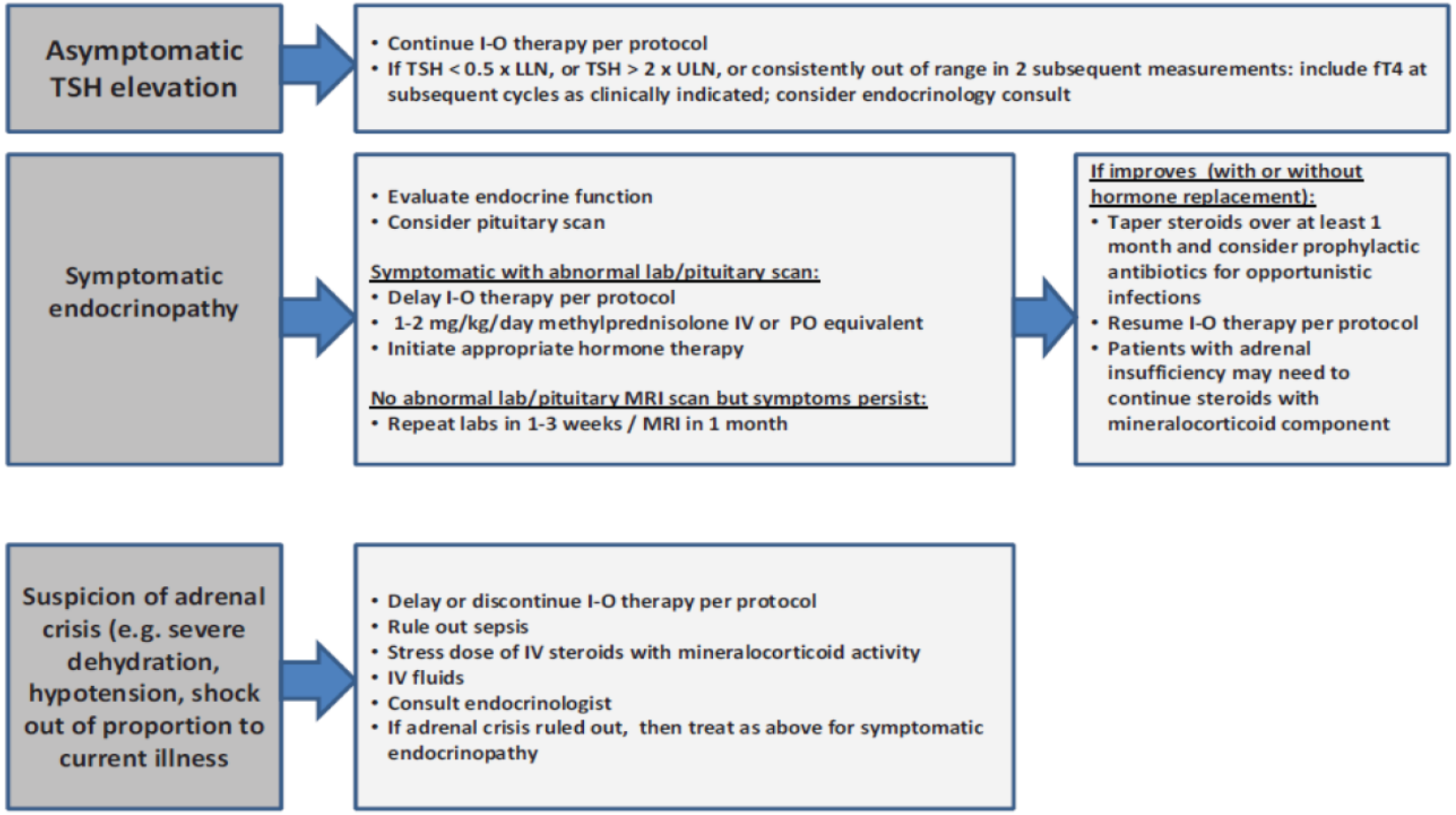

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

# Endocrinopathy Management Algorithm

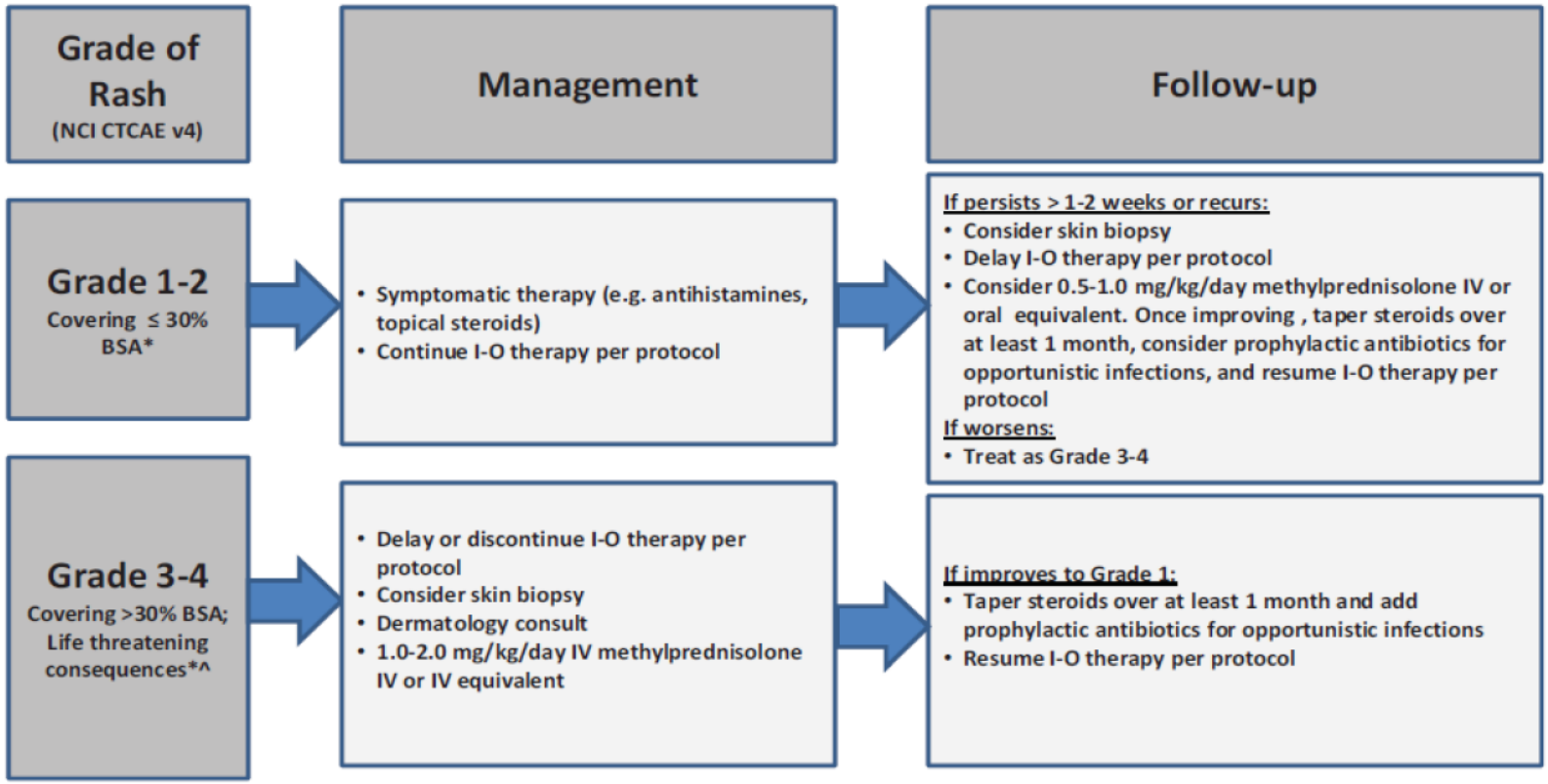
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.




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

# Skin Adverse Event Management Algorithm

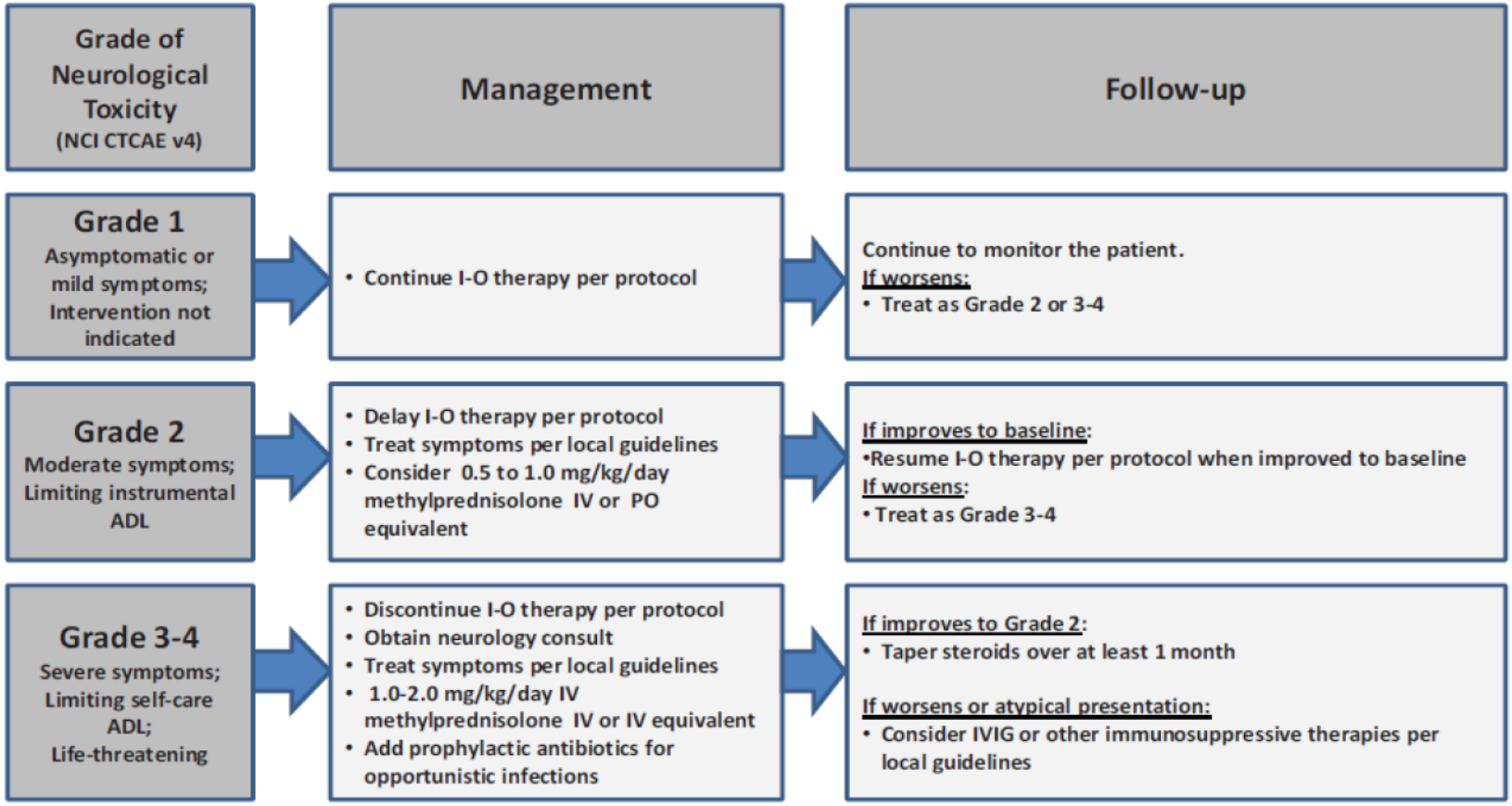
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.




Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

# Neurological Adverse Event Management Algorithm

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




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