A Phase I/II Study of Nivolumab, Ipilimumab and Plinabulin in Patients with Recurrent Small Cell Lung Cancer: Big Ten Cancer Research Consortium BTCRC-LUN17-127

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Patients with Recurrent Small Cell Lung Cancer

VERSION DATE: 27APR2022

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

_____ _____
Signature of Site Investigator Date

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Site Investigator Name (printed)

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Site Investigator Title

_____
Name of Facility

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Location of Facility (City and State)

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BIG TEN CRC ADMINISTRATIVE HEADQUARTERS

SYNOPSIS

TITLE	A Phase I/II Study of Nivolumab, Ipilimumab and Plinabulin in Patients with Recurrent Small Cell Lung Cancer
PHASE	Phase I/II
OBJECTIVES	**Primary:** Phase I: The primary objective of the Phase I dose escalation study is to establish the maximum tolerated dose (MTD) of plinabulin in combination with nivolumab and ipilimumab for patients with recurrent SCLC. Phase 2: The primary objective of the Phase II, single-arm study is to determine if the addition of plinabulin to double checkpoint inhibition (PD-1 and CTLA-4) for recurrent SCLC will improve progression-free survival (PFS, the time from treatment assignment to the date of the first documented tumor progression, or death due to any cause, whichever occurred first). **Secondary:** • To assess toxicity and tolerability of the combination of nivolumab, ipilimumab and plinabulin. • To measure the frequency of immune-related adverse events (irAEs). • To determine the proportion of patients with a confirmed objective response in the Phase II part (defined as the number of patients with a best overall response of complete response or partial response divided by the number of assigned patients). • To estimate clinical benefit rate (CBR: complete response, partial response, or stable disease). • To estimate 6-month (± 4 weeks) PFS. • To estimate overall survival (OS) and 1-year OS. **Exploratory:** • To measure biomarkers of inflammation (high sensitivity C-reactive protein [hsCRP], erythrocyte sedimentation rate [ESR], serum amyloid A [SAA]) and haptoglobin • To correlate tumor mutational burden with PFS and ORR • To measure biomarkers of activity such as immune cell phenotypes, TCR-seq and circulating cytokines and to correlate with PFS and ORR.
STUDY DESIGN	This is an open-label Phase I/II study, with a dose escalation part (Phase I) and a single-arm Phase II, in patients with recurrent SCLC. In the Phase I part, patients will receive plinabulin at escalating doses in combination with nivolumab and ipilimumab. Doses of study drug will be administered as intravenous (IV) infusions in 21-day cycles. Patients will receive all study drugs on Day 1 of each cycle. After 4 treatment cycles, ipilimumab is stopped and patients continue treatment with nivolumab and plinabulin every 2 weeks (maintenance period) or until disease progression, development of unacceptable toxicity or one of the protocol-defined reasons for treatment discontinuation occurs.

	At least 3 patients will be enrolled in each cohort, starting at 20 mg/m^2 of plinabulin. The dose of plinabulin will be escalated in sequential patient cohorts after the safety data from the first cycle is reviewed. Thereafter the dose of plinabulin will be escalated to 30 mg/m^2, provided that dose-limiting toxicities (DLTs) are not observed per the specified criteria, until the RP2D is determined. In the Phase II part, up to 26 patients will be treated with the triple combination of plinabulin (at RP2D) + nivolumab + ipilimumab. Patients will continue treatment until disease progression, development of unacceptable toxicity or one of the protocol-defined reasons for treatment discontinuation occurs.
KEY ELIGIBILITY CRITERIA	1. Must have signed and dated written informed consent form in accordance with regulatory and institutional guidelines. 2. Males and females aged >18 years at time of consent. 3. Histological or cytological confirmed extensive-stage SCLC 4. Patients who progressed after at least 1 platinum-based chemotherapy regimen. Patients with platinum resistance (defined as recurrence or progression of disease within 90 days of completion of the platinum-based regimen) are eligible. For phase II, patients must have been treated with at least one prior line of PD-1/PD-L1 therapy. 5. Measurable disease according to RECIST v1.1 obtained by imaging within 28 days prior to study registration. 6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 within 14 days before registration and minimum life expectancy of at least 12 weeks 7. Treatment to be initiated at least 2 weeks since last dose of prior systemic anticancer therapy (chemotherapy, radiation, and/or surgery) 8. Recovery to grade 1 of any clinically significant toxicity (excluding alopecia, grade 2 fatigue, vitiligo, endocrinopathies on stable replacement therapy) prior to initiation of study drugs 9. Female patients of childbearing potential have a negative pregnancy test at baseline. See Eligibility Criteria for complete guidelines. 10. Adequate laboratory values. a. Absolute neutrophil count ≥1,000/μL. b. Platelet count ≥100,000/μL. c. Hemoglobin ≥9.0 g/dL. d. Total bilirubin ≤1.5 x upper limit of normal (ULN) or ≤3 x ULN for subjects with Gilbert's disease e. ALT and AST ≤3.0 x ULN (≤5 x ULN if evidence of hepatic involvement by malignant disease). f. Creatinine ≤ 1.5 x ULN or estimated glomerular filtration rate ≥40 mL/min/1.73m^2. g. Lipase and amylase ≤1.5 x ULN. Subjects with lipase >1.5 x ULN may enroll if there are neither clinical nor radiographic signs of a pancreatitis. 11. Must not have received previous CTLA-4 targeted therapy.

STATISTICAL CONSIDERATIONS	**Sample Size** For the Phase I part of the study, between 9 and 15 patients will be enrolled. For the Phase II portion of the study, PFS will be the primary outcome. The patients will receive nivolumab, ipilimumab and plinabulin. In previous studies, without plinabulin, the median survival with nivolumab and ipilimumab was 1.5 months. It is anticipated to be able to detect, with 80% power, an increase in PFS from 1.5 to 3.5 months (a 2 month increase), with a two sided 5% level test of survival. Assuming an accrual period of 12 months and an additional 1 year of follow-up time, this increase could be detected by accruing 26. Patients who receive plinabulin at RP2D level in phase I dose-escalation will count towards the 26 patients and will be included in the efficacy analysis. **Safety Endpoints** The safety endpoints for this study are the incidence and severity of AEs and laboratory abnormalities, the occurrence of SAEs and treatment discontinuations due to AEs. **Efficacy Endpoints** Primary Efficacy Endpoint: • PFS in the Phase II part of the study. Secondary Efficacy Endpoints: • Objective response in the Phase II part of the study. • CBR: complete response, partial response, or stable disease. • 6-month PFS. • OS and 1-year OS. **Analysis Populations** Safety Population: all patients who received at least 1 dose of plinabulin, nivolumab and ipilimumab and had at least 1 post-dose safety assessment. DLT Evaluable Population: all patients in the dose-escalation part who received 2 doses of plinabulin, nivolumab and ipilimumab. Efficacy Evaluable Population: all patients who received RP2D of plinabulin and met the following two criteria will be considered evaluable for efficacy: • patients who received at least 1 cycle of therapy • patients who had at least 1 on-study disease assessment or who developed early progression prior to the first planned on-study disease assessment.
TOTAL NUMBER OF SUBJECTS	Phase I: approximately 9-15 patients Phase II: up to 26 patients
ESTIMATED ENROLLMENT PERIOD	Phase I: 6-9 months Phase II: 12 months
ESTIMATED STUDY DURATION	36 months

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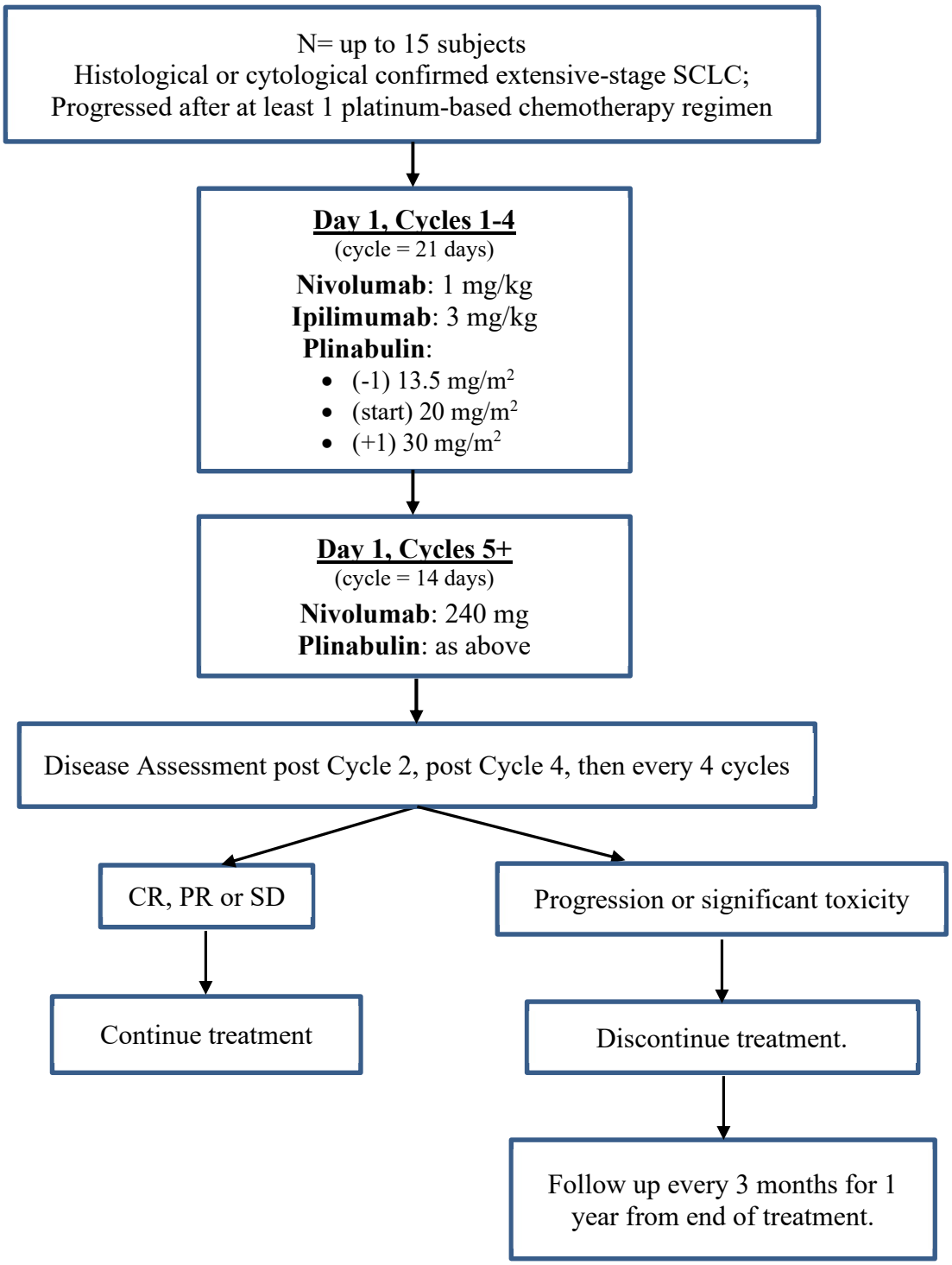
LIST OF ABBREVIATIONS

5-HT_3	5-Hydroxytryptamine Type 3
ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
ALT (SGPT)	Alanine Aminotransferase
AST (SGOT)	Aspartate Aminotransferase
BSA	Body Surface Area
CBC	Complete Blood Count
CI	Confidence Interval
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DSMC	Data Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form(s)
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HIV	Human Immunodeficiency Virus
hsCRP	High Sensitivity C-reactive Protein
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Institutional Ethics Committee
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous

LIST OF ABBREVIATIONS

irAE(s)	Immune-related Adverse Event(s)
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not Evaluable
OR	Objective Response
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive Disease
PDE4	Phosphodiesterase Type 4
PFS	Progression-free Survival
PR	Partial Response
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAA	Serum Amyloid A
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCLC	Small Cell Lung Cancer
T3	Triiodothyronine
T4	Free Thyroxine
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell
WHO	World Health Organization

PHASE I SCHEMA



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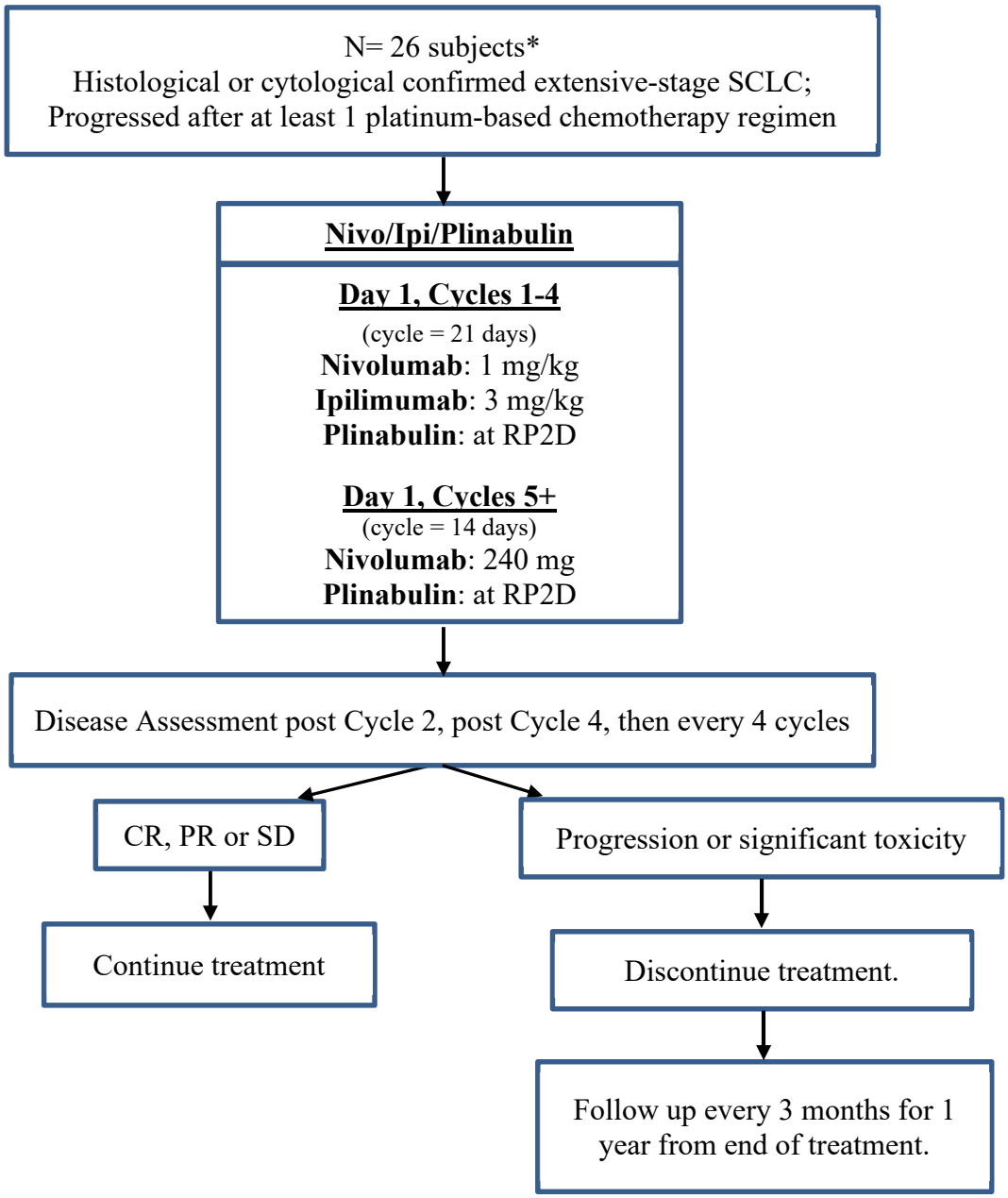

* Patients who receive plinabulin at the recommended phase 2 dose (RP2D) level in the phase I dose-escalation will count towards the 26 patients.

1. BACKGROUND AND RATIONALE

1.1 Rationale for the study

Lung cancer is the leading cause of cancer-related mortality worldwide. According to WHO Fact Sheet no 297, updated February 2017, lung cancer caused 1.69 million deaths in 2015. In the United States (US), approximately 415,000 Americans living today have been diagnosed with lung cancer at some point in their lives (U.S. National Institutes of Health, 1975-2013). During 2016, an estimated 224,390 new cases of lung cancer were expected to be diagnosed, representing about 13 percent of all cancer diagnoses (Siegel et al 2016). Neuroendocrine tumors account for approximately 20% of lung cancers; most of which (approximately 14%) are SCLC. In 2017, an estimated 31,000 new cases of SCLC will occur in the US (Siegel et al 2017). SCLC is characterized by a rapid doubling time, high growth fraction and early development of widespread metastases. Most patients with SCLC present with hematogeneous metastases; approximately one-third present with limited disease confined to the chest. SCLC is highly sensitive to initial chemotherapy and radiotherapy; however, most patients eventually die of recurrent disease (Jett et al 2013). Estimated deaths from this disease are approximately 4% of all cancer mortality (Jemal et al 2011). Median survival for patients treated with chemotherapy is approximately 12.7-12.9 months for limited-stage and 7.3 months for extensive-stage disease (Powell et al 2014, Jhun et al 2013). In 2018, a phase 3 trial (Impower133) reported an improvement in median overall survival when anti-PD-L1 antibody, atezolizumab was used in combination with chemotherapy compared to chemotherapy alone (12.3 months vs. 10.3 months, p=0.0007) for the first-line treatment of extensive-stage SCLC (Horn et al 2018). At the time of data cutoff at median follow-up of 13.9 months, 94% patients had progressed or died in the chemotherapy alone arm. Addition of atezolizumab improved this number to only 85% demonstrating that majority of patients with extensive-stage SCLC eventually progress.

One reason for the poor prognosis is due to limited treatment options for patients with recurrent disease. Recommended systemic therapy agents for patients with recurrent SCLC include topotecan, irinotecan, etoposide and gemcitabine (Jett et al 2013). However, the response rates with these regimens are less than 10% to 15% with median PFS of less than 3 months. Recently, nivolumab with or without ipilumumab has been added to the NCCN guidelines as an option for recurrent disease. Nivolumab is an antibody that targets PD-1 and ipilumumab is an antibody targeting CTLA4, two immune checkpoints crucial for tumor growth. These recommendations are based on a phase 1/2 trial which reported response rate of 10% with nivolumab alone and 19% to 23% with the combination. Overall frequency of grade 3 or 4 adverse events (AEs) was about 20% and the median PFS was 2.6 months with the combination (Antonia et al 2016).

Plinabulin (BPI-2358), a synthetic analogue of the chemical halimide isolated from a marine fungus, is a vascular disrupting agent with pleomorphic immune effects, notably promoting the maturation of dendritic cells. Plinabulin induces tumor regression alone and synergistically with other standard chemotherapeutic agents in tumor models (Bertelsen et al 2011). Plinabulin has immune-enhancing effects through stimulation of dendritic cells, and antigen-specific CD4 T cell proliferation. In addition, plinabulin has pro-apoptotic effects on tumor cells, and reduces tumor blood flow. In preclinical models, the addition of plinabulin to PD1-inhibitors and CTLA4-inhibitors inhibits tumor growth approximately two-fold more than the PD1/CTLA4-inhibitor combination. Plinabulin also has anti-inflammatory effects through phosphodiesterase type 4 (PDE4)-inhibition, which may reduce immune-related AEs (irAEs), since PDE4 is a proven target for inflammation.

In a phase 1 first-in-human trial in 38 patients, plinabulin (at the RP2D of 30 mg/m²), showed a favorable safety profile, while eliciting biological effects as evidenced by decreases in tumor blood flow, tumor pain, and other mechanistically relevant AEs (Mita et al 2010). Findings from a phase 2 trial investigating the combination of plinabulin and docetaxel compared to docetaxel alone in patients with advanced non-small cell lung cancer (NSCLC) was presented at the ASCO-SITC Clinical Symposium in February, 2017 (Mohanlal et al 2017). In addition to a trend towards a survival benefit in 76 patients with measurable disease (11.3 vs 6.7 months), plinabulin also protected against the development of docetaxel-induced AEs, especially neutropenia. The rate of grade 4 neutropenia was only 3% to 5% in the combination arm compared to 33% in the docetaxel alone arm ($p < 0.0003$). Based on these findings, the global phase 3 DUBLIN-3 trial has been initiated to evaluate second- or third-line treatment with docetaxel plus plinabulin versus docetaxel in patients with advanced NSCLC.

This study investigates the hypothesis that combining plinabulin with double checkpoint inhibition with anti-PD1 and anti-CTLA4 antibodies (nivolumab and ipilimumab respectively) will improve PFS as well as prevent irAEs, in patients with recurrent SCLC.

1.2 Plinabulin (BPI-2358, previously known as NPI-2358)

Plinabulin (BPI-2358) is a synthetic, low molecular weight, new chemical entity originally developed by Nereus Pharmaceuticals, Inc., and now by BeyondSpring Pharmaceuticals, Inc. It belongs to the diketopiperazine class of compounds with a chemical name 2, 5-piperazinedione, 3-[[5-(1,1-dimethylethyl)-1H-imidazol-4-yl[methylene]-6-(phenylmethylene)-, (3Z,6Z) (trivial name t-butyl-dehydrophenylahistin).

Plinabulin attacks cancer growth via several mechanisms. It inhibits angiogenesis, causes collapse of the existing tumor vasculature as well as directly inducing cancer cell apoptosis via the Ras-JNK pathway (Singh 2011). Furthermore, plinabulin enhances immune system function, inducing dendritic cell maturation, decreasing the regulatory T cell population and increasing the relative proportion of tumor-killing CD8+ T cells and enhances CD4+ T-cell proliferation. Based on *in vitro* and *in vivo* nonclinical studies, plinabulin appears to have several advantages over other agents, namely; 1) multiple intrinsic anti-tumor actions, including a direct cytotoxic effect through the Ras-JNK pathway; 2) long-lasting (>24 hours) reduction in tumor blood flow; 3) anti-tumor effects against both small and large tumors; 4) enhancement of the tumor-relevant immune system function and 5) sustained inhibition on tumor growth after cessation of treatment. Thus, plinabulin could be an effective treatment for recurrent SCLC when administered in combination with anti-PD1 and anti-CTLA4 antibodies (nivolumab and ipilimumab, respectively).

Plinabulin also exerts PDE4-inhibitory activity, which is associated with anti-inflammatory effects. PDE4-inhibitor drugs are approved to treat a number of inflammatory disorders, such as psoriasis, eczema, and chronic obstructive pulmonary disease. Thus Plinabulin has a unique profile, in that it is expected to exert immune-enhancing effects (through dendritic cell activation), while exerting anti-inflammatory effects (through PDE4-inhibition). In addition, Plinabulin also has direct anti-cancer effects as outlined in the section below.

1.2.1 Pharmacology

Plinabulin exerts a marked inhibition of tubulin polymerization, resulting in shortening of newly formed tubulin polymer and disruption of the fine network of α-tubulin network in human umbilical vein endothelial cells (HuVECs, a model for tumor vascular endothelium) and tumor cells. In contrast to

vinca and taxane chemotherapeutics, plinabulin induces tubulin depolymerization without altering microtubule dynamics. This observation suggests that plinabulin could induce mitotic block with minimal disruption of other microtubule functions (e.g., axonal flow). In addition, plinabulin increases HuVEC permeability to high molecular weight molecules such as dextran, resulting in endothelial cell swelling, increasing vascular permeability and disruption of tumor blood flow. The combination of tumor vascular cell swelling which produces a hemorrhagic necrosis of the tumor, a direct cytotoxic effect on tumor cells through the Ras-JNK pathway, and inhibition of tumor angiogenesis results in a highly effective anti-tumor activity observed with this agent (Nicholson 2006, Singh 2011). Compounds which inhibit tubulin polymerization enhance immune function and synergize with immune checkpoint inhibitors in immune competent animal models (Martin et al 2014, Müller et al 2014). Plinabulin enhances immune system function as demonstrated by increased maturation of dendritic cells *in vitro* and by enhancing with immune checkpoint inhibitors and regulating T-cell function *in vivo* (Lloyd et al 2016).

Utilizing rodent models to assess tumor blood flow and tumor viability, plinabulin was shown to induce a highly selective and rapid vascular collapse and disruption of blood flow leading to central tumor necrosis without an observed effect on the vasculature in the surrounding fat pad or non-tumor tissues such as heart, lungs, and skeletal muscle. Alterations in tumor blood flow and morphology were associated with regression in tumor size. Plinabulin exerted potent cytotoxicity directly against tumor cell lines *in vitro*. The human HT-29 (colon), PC-3 (prostate), MDA-MB-231 (breast), RPMI-8226 (multiple myeloma), and NCI-H292 (NSCLC) tumor cell lines were similarly sensitive with 50% inhibitory concentrations (IC_{50}) ranging from 10 to 18 nM. This intrinsic cytotoxic effect was a result of mitotic block and the induction of apoptosis as evidenced by PARP cleavage, activation of caspase-3, -8, and -9 in multiple myeloma model.

In vitro investigation in paclitaxel- or mitoxantrone-sensitive and resistant cell lines respectively, showed that the potency of plinabulin was not affected by the mechanisms for drug resistance to either paclitaxel (overexpression of P-glycoprotein) or mitoxantrone (decrease of topoisomerase II activity). Thus, it appears that the cytotoxicity of plinabulin on tumor cells was independent of common drug resistance mechanisms, suggesting its potential role in treating refractory or resistant diseases.

In vivo tumor models in mice and rats demonstrated both single agent activity (e.g., against breast tumors, sarcomas, and multiple myeloma) and marked potentiation of common chemotherapeutics (e.g., against prostate, NSCLC, and colon carcinomas), and with radiation (in a mouse sarcoma model). Notably, plinabulin significantly enhanced the anti-tumor effect of docetaxel in a human NSCLC model of large tumors. The combination was observed to be better tolerated than docetaxel alone. In immune competent mice (MC-38 colon tumor model), plinabulin alone enhances immune system function and enhances the anti-tumor activity of immune checkpoint inhibitors.

1.2.2 Pharmacokinetics and Drug Disposition

The pharmacokinetics of plinabulin after intravenous (IV) administration was evaluated in the rat, dog, and monkey. The results of these studies demonstrated dose-dependency for AUC and C_{max}. The elimination half-life ($t_{½}$) was dose-independent. The $t_{½}$ for plinabulin ranged from 1 to 2 hours in these species.

In vitro microsome assays were performed to investigate metabolism of plinabulin. There was very little degradation of plinabulin observed over a 2-hour incubation period in human, dog, monkey, and rodent liver microsomes with or without metabolic activation. No metabolites of plinabulin have been

identified. Furthermore, plinabulin was a weak CYP inhibitor. It was not known whether plinabulin was a CYP substrate. The disappearance of plinabulin *in vitro* using human liver microsomes indicates slight metabolism that may be P450-mediated (mean 93% plinabulin remaining). The metabolic pathway has not yet been determined. When plinabulin was evaluated for P450 CYP inhibition in human liver enzymes, the mean (of 2 studies) percent inhibitions were 37% for CYP1A2, 60% for CYP2C9, 15% for CYP2C19, 17% for CYP2D6, and 12% for CYP3A4, at a concentration of 10 μM plinabulin, which was unlikely to be attained in humans clinically. Drug-drug interaction with commonly used medication was deemed unlikely.

Plinabulin was 95% bound to human plasma proteins. In a mass distribution study in rats with ^{14}C-plinabulin, quantitative whole body autoradioluminography showed that the radioactivity distributed rapidly with the highest concentrations located in the wall of the small intestine, liver, kidney, and adrenals. Central nervous system (CNS), eye and bone exhibited C_{max} below blood levels. The administered dose was excreted mainly via the urine, with contribution from fecal elimination. A total of 7 metabolites were detected in plasma, urine, and feces. The major metabolite was similar in blood and urine, but different in feces. The metabolites have not been characterized.

1.2.3 Toxicology and Safety Pharmacology

The toxicology for plinabulin was studied in rats, dogs and monkeys. In the initial series of studies, the high concentration of organic solvent used in drug preparation for these studies contributed to the observed toxicology findings. These studies included the GLP IND-enabling toxicology study in dogs. After the toxic effect of solvent in vehicle was discovered, subsequent toxicology studies employed preparations with lower solvent concentration to test the plinabulin-specific toxicity. In the cardiac safety studies in the monkey, the vehicle used was closely approaching that used in clinical studies, and was without effect except for a slight (4-5%) transient reduction in heart rate. In the pivotal GLP toxicity study in the monkey, on the last day of dosing (but not on Day 1 or after the recovery period) minimal cardiac (44% increase in R-R and 10% increase in Q-T intervals without apparent change in the QTc interval) and cardiovascular (18% decrease in heart rate) effects were observed in the animals receiving 42 mg/m^2.

From the GLP pivotal toxicity study in rats and monkeys (3 months, ICH S9 guidelines), GLP Investigational New Drug (IND)-enabling toxicology studies in the rat and dog, the echocardiography studies in dogs and monkeys, and from the reports of studies with other agents having the similar mechanism of action, the following are potential target organs for plinabulin:

- Cardiovascular: Cardiovascular effects and cardiotoxicity have been reported for compounds that stabilize microtubule polymerization and reduce tumor blood flow. Cardiotoxicity was observed in toxicity studies for plinabulin in the rat and dog but not in nonhuman primates, even at very high doses.
- Gastrointestinal tract
- Nervous system
- Bone marrow
- Liver
- Kidney
- Injection site
- Reproductive organs
- Allergic reactions

These findings were generally reversible at all doses, including those characterized as severely toxic, except for the decreased body weight/food consumption, cardiac fibrosis, and testicular changes. It is worth pointing out that the above safety findings were made in studies using vehicle containing high concentration of organic solvent. The organic solvent used in vehicle for drug preparation in the clinical study would be 20-to 200-fold lower than it was in the above animal studies, potentially providing an additional margin of safety.

1.2.4 Previous Clinical Experience with Plinabulin

Two clinical studies with plinabulin have been conducted to date, a Phase 1 monotherapy study and a Phase 1/2 combination study with docetaxel in NSCLC. A total of 141 patients with advanced cancer received plinabulin.

Study NPI-2358-100 was a Phase 1, open-label, dose-escalation study to determine the maximum-tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of plinabulin monotherapy in patients with advanced malignancies whose disease had progressed after treatment with standard treatments. Plinabulin was administered once per week (2 to 30 mg/m^2) as an IV infusion for 3 successive weeks in repeating 4-week cycles. A total of 38 patients received plinabulin monotherapy (Mita 2010).

Pharmacokinetic analysis demonstrated a linear increase in C_{max} and AUC with dose. The $t_{½}$ was approximately 6 hours. Pharmacodynamics was evaluated utilizing dynamic contrast-enhanced MRI which demonstrated decreases in K_{trans} (a marker for tumor blood flow) at doses above 13.5 mg/m^2. The decrease of tumor blood flow was dose dependent, with the greatest tumor flow decrease of 82% at 30 mg/m^2.

Plinabulin was generally well tolerated. AEs occurring in ≥20% of patients included nausea (61%), vomiting (47%), diarrhea and fatigue (34% respectively), constipation, pyrexia, and headache (26% respectively), anorexia (24%), and anemia (21%). Overall, 16 patients (42%) experienced serious adverse events (SAEs), the majority were considered not related to plinabulin. The RP2D was determined to be 30 mg/m^2. While no patient achieved a CR or PR, the proportion of patients with stable disease appeared to have increased with increasing plinabulin doses. A total of 7 (47%) out of 18 evaluable patients achieved stable disease at the RP2D level (30 mg/m^2).

Study NPI-2358-101 was a Phase 1/2, open-label study to evaluate plinabulin in combination with docetaxel in patients with advanced NSCLC that had progressed after treatment with at least 1 chemotherapy regimen. Study medication was administered by IV infusion on Day 1 (docetaxel and plinabulin) and Day 8 (plinabulin) of each 3-week cycle. The Phase 1 portion of the study investigated the safety of plinabulin/docetaxel (DN) combination with docetaxel dose fixed at the standard 75 mg/m^2 for NSCLC. Thirteen patients were enrolled sequentially in cohorts of plinabulin escalating from 13.5 mg/m^2 to 30 mg/m^2. The RP2D of plinabulin was determined to be 30 mg/m^2. The Phase 2 portion of the study explored the plinabulin effect on efficacy by comparing DN combination to docetaxel (D) alone. Patients were randomized to receive either docetaxel (75 mg/m^2) in combination with plinabulin (30 mg/m^2 or 20 mg/m^2) or docetaxel (75 mg/m^2) alone. A total of 90 patients (50 received plinabulin 30 mg/m^2, and 40 20 mg/m^2, respectively) were randomized to the DN arm versus 73 patients to D arm. For the 30 mg/m^2 Cohort, based on the intent-to-treat (ITT) analysis, the median overall survival (OS) was 8.7 months in DN, and 7.5 months in D arm. The Hazard ratio (HR) was 0.97 with a p-value of 0.89. The objective response (OR) rate was 14.0% for DN and 14.5% for D; however, the median duration of response (DoR; which is a marker of immune enhancing activity), in patients receiving DN was 12.7 months compared to the median of 1.5 months in patients receiving D alone. The improvement of DoR

was statistically significant (p=0.049) (Millward et al 2012). A comparable improvement in DoR was observed with the 20 mg/m plinabulin dose. For the subgroup of patients with a measurable lung lesion (RECIST 1.1), the DN arm (n=38) had an mOS benefit of 4.6 months longer vs D alone (n=38), with the 30 mg/m^2 plinabulin dose (Mohanlal et al 2017).

Plinabulin was found to be generally well tolerated in combination with docetaxel. The combination appeared to have a similar AE profile as single-agent docetaxel. In patients receiving DN at 30 mg/m^2 of plinabulin (RP2D), the most common AEs regardless of causality were diarrhea (58%), fatigue (52%), nausea (48%), constipation (36%), vomiting (34%), anorexia (34%), and hypertension (32%). The increase in gastrointestinal (GI)-related AEs is consistent with PDE4-inhibition, which is known to increase frequency of nausea, vomiting and diarrhea. In addition a dose-dependent increase in 'steroid'-related AEs was observed, which is also suggestive of PDE4-inhibition with plinabulin. Unexpectedly, a significantly lower rate of neutropenia (all events and events ≥ grade 3) was observed in patients in DN arm than in D arm (p≤0.01). The use of granulocyte-colony stimulating factor and the rate of docetaxel dose reduction were also lower in DN than in D arm.

Although there was no difference in the median duration of overall survival on the DN and D arms based on the ITT analysis, a *post hoc* exploratory analysis identified a subset (described below) of patients who appeared to benefit from treatment with plinabulin.

1.3 Nivolumab

Nivolumab is a fully human anti-PD-1 IgG4 monoclonal antibody. The PD-1/PD-L1 pathway is a crucial self-tolerance pathway that tumor cells hijack to escape immune elimination. The PD-1/PD-L1 interaction inhibits T-cell response, induces apoptosis of tumor-specific T cells, and promotes differentiation of CD4 T cells into Tregs and tumor cell resistance (Aerts et al 2013). PD-1 is expressed on the surface of activated T cells, B cells, and natural killer cells (Agata et al 1996). Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy and in combination with ipilimumab in several tumor types, including NSCLC, melanoma, renal cell carcinoma, classical Hodgkin Lymphoma, SCLC, gastric cancer, urothelial cancer, hepatocellular carcinoma, and colorectal cancer. Nivolumab is approved for use in multiple countries including the United States. Warnings for nivolumab include immune-mediated reactions, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, rash, and encephalitis, as well as infusion reactions and embryo-fetal toxicity. The most common adverse reactions (≥20%) in patients with melanoma were fatigue, rash, musculoskeletal pain, pruritus, diarrhea, and nausea as a single agent, and fatigue, rash, diarrhea, nausea, pyrexia, vomiting, and dyspnea when administered with ipilimumab. In metastatic non-small cell lung cancer (NSCLC), the most common adverse reactions (≥20%) were fatigue, musculoskeletal pain, decreased appetite, cough, and constipation (BMS 2016).

The pharmacokinetics (PK) of nivolumab were studied in subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. Nivolumab clearance (CL) decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of approximately 24.5% (47.6%) resulting in a geometric mean steady state clearance (CLss) (CV%) of 8.2 mL/h (53.9%); the decrease in CLss is not considered clinically relevant. The geometric mean volume of distribution at steady state (Vss) was 6.8 L (27.3%), and geometric mean elimination half-life ($t_{1/2}$) was 25 days (77.5%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg q2w, and systemic accumulation was approximately 3.7-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg

administered every 2 weeks. Additionally, nivolumab has a low potential for drug-drug interactions. The clearance of nivolumab increased with increasing body weight. The population PK (PPK) analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1, solid tumor type, baseline tumor size, and hepatic impairment.

1.4 Ipilimumab

Ipilimumab is a fully humanized monoclonal antibody (mAb) against the CTLA-4 epitope that neutralizes the receptor, thus enabling cytotoxic T cell activity and perpetuating immune responses. Most of the benefits of anti CTLA- 4 blockade seem to be mediated by depletion of T-regulatory (Treg) cells as these cells demonstrate high levels of CTLA-4 expression (Peggs et al 2009). Ipilimumab is being investigated both as monotherapy and in combination with other modalities such as chemotherapy, radiation therapy, and other immunotherapies. Ipilimumab is approved for the treatment of melanoma in multiple countries. Warnings for ipilimumab include immune-mediated reactions, including hepatitis and endocrinopathies, as well as embryo-fetal toxicity. The most common adverse reactions (≥5%) have been fatigue, diarrhea, pruritus, rash, and colitis. At the 10 mg/kg dose (higher than anticipated in this study), additional common adverse reactions (≥5%) include nausea, vomiting, headache, weight loss, pyrexia, decreased appetite, and insomnia (BMS 2015).

The PK of ipilimumab has been extensively studied in subjects with melanoma, at the 3- and 10-mg/kg doses administered as a 1.5-hour IV infusion. The PK of ipilimumab was characterized by PPK analysis and determined to be linear and time invariant in the dose range of 0.3 to 10 mg/kg. The summary of PK parameters after single and multiple doses of ipilimumab in subjects with advanced melanoma from Studies MDX010-15, CA184007, and CA184008 (with intensive PK samples available) are listed in Table 5.2.1-1 of the Ipilimumab IB. The PPK of ipilimumab was studied in 785 subjects (3200 serum concentrations) with advanced melanoma in 4 Phase 2 studies (CA184004, CA184007, CA184008, and CA184022), 1 Phase 3 study (CA184024), and 1 Phase 1 study (CA184078). The PPK analysis demonstrated that the PK of ipilimumab is linear, the exposures are dose proportional across the tested dose range of 0.3 to 10 mg/kg, and the model parameters are time-invariant, similar to that determined by noncompartmental analyses. Upon repeated dosing of ipilimumab, administered every 3 weeks (q3w), minimal systemic accumulation was observed by an accumulation index of 1.5-fold or less, and ipilimumab steady-state concentrations were achieved by the third dose. The ipilimumab CL of 16.8 mL/h from PPK analysis is consistent with that determined by noncompartmental PK analysis and shown in Table 5.2.1-1 of the Ipilimumab IB. The terminal T1/2 and Vss of ipilimumab calculated from the model were 15.4 days and 7.47 L, respectively, which are consistent with that determined by noncompartmental analysis. Volume of central compartment (Vc) and peripheral compartment were found to be 4.35 and 3.28 L, respectively, suggesting that ipilimumab first distributes into plasma volume and, subsequently, into extracellular fluid space. CL of ipilimumab and Vc were found to increase with increase in body weight. However, there was no significant increase in exposure with increase in body weight when dosed on a milligram/kilogram basis, supporting dosing of ipilimumab based on a weight normalized regimen. The PK of ipilimumab is not affected by age, gender, race, and immunogenicity (anti-drug antibody [ADA] status); concomitant use of chemotherapy, prior therapy, body weight, performance status; or tumor type.

1.5 Nivolumab and Ipilimumab Combination

In CA209004, a Phase 1B dose-escalation study of nivolumab in combination with ipilimumab in subjects with unresectable stage III or IV malignant melanoma, the 3 mg/kg nivolumab and 3 mg/kg ipilimumab cohort exceeded the MTD per protocol. While both Cohort 2 (1 mg/kg nivolumab + 3 mg/kg ipilimumab) and Cohort 2a (3 mg/kg nivolumab + 1 mg/kg ipilimumab) had similar clinical activity, a dose of 3 mg/kg of ipilimumab q3w for a total of 4 doses and 1 mg/kg nivolumab q3w for 4 doses followed by nivolumab 3mg/kg every 2 weeks (q2w) until progression, was chosen. Exposure-response analysis of nivolumab monotherapy across dose ranges of 1 mg/kg to 10 mg/kg reveals similar clinical activity while exposure-response analysis of 0.3 mg/kg, 3 mg/kg, and 10 mg/kg of ipilimumab monotherapy have demonstrated increasing activity with increase in dose in the Phase 2 study CA184022 (Wolchok et al 2009). Therefore, the selection of 3 mg/kg of ipilimumab (Cohort 2) may be more clinically impactful than selection of 3 mg/kg of nivolumab (Cohort 2a). Data from the Phase 3 study CA209067 in subjects with advanced melanoma showed that the administration schedule of 1 mg/kg of nivolumab q3w plus 3 mg/kg of ipilimumab q3w for 4 doses, followed by 3 mg/kg of nivolumab q2w for cycle 3 and beyond is safe and well tolerated (Larkin et al 2015). Anti-CTLA4 targeted therapy has been reported to be efficacious also in patients with resistance to prior anti-PD-1/PD-L1 therapy in multiple retrospective studies (Zimmer et al 2017, Jacobsoone-Ulrich et al 2016, Aya et al 2016). Multiple trials are now ongoing with PD-1/PD-L1 targeted therapy and ipilimumab to investigate the efficacy of this combination in patients with primary or secondary resistance to immunotherapy.

In a Phase 1/2 study by Antonia et al, nivolumab with or without ipilimumab showed antitumor activity with durable responses and manageable safety profiles in previously treated patients with SCLC: nivolumab 3 mg/kg q2w achieved a PR and stable disease (SD) in 10% (10/98) and 22% (22/98), respectively, while the combination of nivolumab and ipilimumab (1 and 1 mg/kg, 1 and 3 mg/kg, or 3 and 1 mg/kg, respectively) q3w x 4 followed by nivolumab 3 mg/kg q2w achieved an objective response rate (ORR) and SD in 23% (14/61) and 19% (10/54), respectively (Antonia et al 2016). Treatment was generally well tolerated, with grade 3 or higher treatment-related AEs occurring in 13 (13%) patients in the nivolumab 3 mg/kg cohort, 18 (30%) in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg cohort, and 10 (19%) in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg cohort; the most commonly reported grade 3 or 4 treatment-related AEs were increased lipase (none vs. 5 [8%] vs. none) and diarrhea (none vs. 3 [5%] vs. 1 [2%]). No patients in the nivolumab 1 mg/kg plus ipilimumab 1 mg/kg cohort had a grade 3 or 4 treatment-related AE. Six (6%) patients in the nivolumab 3 mg/kg group, 7 (11%) in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg group, and 4 (7%) patients in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg group discontinued treatment due to treatment-related AEs. Two patients who received nivolumab 1 mg/kg plus ipilimumab 3 mg/kg died from treatment-related AEs (myasthenia gravis and worsening of renal failure), and 1 patient who received nivolumab 3 mg/kg plus ipilimumab 1 mg/kg died from treatment-related pneumonitis. Nivolumab and the combination of nivolumab and ipilimumab, therefore, appear to have clinically significant therapeutic potential in SCLC (Antonia et al 2016).

1.5.1 Rational for Nivolumab and Ipilimumab Dosing

CheckMate 032 was a phase I/II trial that evaluated multiple regimens of nivolumab in combination with ipilimumab in solid tumors, including advanced SCLC. There were four initial treatment arms: patients with advanced SCLC and disease progression after prior platinum-based chemotherapy were assigned to nivolumab (3 mg/kg Q2W; n = 98), nivolumab 1 + ipilimumab 1 (n=3), nivolumab 1 +

ipilimumab 3 (1 mg/kg and 3 mg/kg Q3W x 4, then nivolumab 3 Q2W; n = 61) and nivolumab 3 + ipilimumab 1 (n=54). Safety and efficacy was assessed with a follow-up of 18 months. The early results from the four initial treatment arms were reported by Antonia et al in 2016 as described above (Antonia et al 2016). Grade 3 or 4 treatment-related AEs occurred in 13% patients in the nivolumab 3 mg/kg cohort, 30% in the nivolumab 1 + ipilimumab 3 cohort, and 19% in the nivolumab 3 + ipilimumab 1 cohort. Six percent of the patients in the nivolumab 3 mg/kg group, 11% in the nivolumab 1 + ipilimumab 3 group, and 7% in the nivolumab 3 + ipilimumab 1 group discontinued treatment due to treatment-related adverse events. Two patients who received nivolumab 1 + ipilimumab 3 mg/kg died from treatment-related AEs (myasthenia gravis and worsening of renal failure), and one patient who received nivolumab 3 + ipilimumab 1 died from treatment-related pneumonitis. Based on these results from the initial four treatment arms, it was determined to use nivolumab 1 + ipilimumab 3 for the subsequent expansion for this combination. For the expansion cohort, patients were randomized 3:2 to nivolumab vs nivolumab 1 + ipilimumab 3 and stratified by a number of prior therapies. A total of 247 pts were randomized to the two arms. Preliminary results from the randomized expansion were reported by Hellmann et al at the annual ASCO meeting in Chicago in June 2017 (Hellmann MD, Ott PA, Zugazagoitia J, et al. First report of a randomized expansion cohort from CheckMate 032, J Clin Oncol 2017;35: Abstract 8503). Of the 159 patients who were evaluable, 98 received nivolumab only and 61 received nivolumab 1 + ipilimumab 3. The ORR was 11% in the nivolumab arm vs. 25% in the combination arm. The combination of nivolumab 1 + ipilimumab 3 was well tolerated with 33% of the patients experiencing grade 3-4 treatment related adverse event (vs. 14% in the nivolumab only arm) and 11% discontinuing treatment due to adverse events. Based on the safety and efficacy date from initial results and follow-up expansion cohort from CheckMate 032, the combination of nivoumab 1 + Ipilimumab 3 has been included as a second-line (or beyond) option for the treatment of recurrent SCLC in the *NCCN* guidelines for SCLC. In our study, we will therefore use the nivolumab 1 + ipilimumab 3 dosing regimen in combination with escalating dose cohorts of plinabulin.

1.6 Nivolumab, Ipilimumab and Plinabulin Combination

Plinabulin induces tumor regression alone and synergistically with other standard chemotherapeutic agents in tumor models (Bertelsen et al 2011). Plinabulin has immune-enhancing effects through stimulation of dendritic cells, and antigen-specific CD4 T cell proliferation. In addition, plinabulin has pro-apoptotic effects on tumor cells, and reduces tumor blood flow. In preclinical models, the addition of plinabulin to PD1-inhibitors and CTLA4-inhibitors inhibits tumor growth approximately two-fold more than the PD-1/CTLA4-inhibitor combination only. Therefore, in our study, we aim to test the hypothesis that the combination of PD-1 and CTLA-4 inhibition will be synergistic with plinabulin. Moreover, Plinabulin has anti-inflammatory effects through phosphodiesterase type 4 (PDE4)-inhibition, which may reduce immune-related adverse events, since PDE4 is a proven target for inflammation. Therefore, we hypothesize that combination of plinabulin with PD-1/CTLA4 combination may result in fewer immune-related side effects leading to better tolerance and fewer treatment discontinuation of the immunotherapy regimen. The overall goal of this study is to investigate if combining plinabulin with double checkpoint inhibition with anti-PD1 and anti-CTLA4 antibodies (nivolumab and ipilimumab respectively) will improve PFS as well as prevent irAEs, in patients with recurrent SCLC.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

This study will be conducted in two parts: a Phase I dose escalation part and a Phase II part.

2.1.1 Primary Objective

Phase I:

- The primary objective of the Phase I dose escalation study is to establish the MTD of plinabulin in combination with nivolumab and ipilimumab for patients with recurrent SCLC.

Phase II:

- The primary objective of the Phase II, single arm study is to determine if the addition of plinabulin (at the 30 mg/m^2 dose) to double checkpoint inhibition (PD-1 and CTLA-4) for recurrent SCLC will improve PFS (the time from treatment assignment to the date of the first documented tumor progression, or death due to any cause, whichever occurred first).

2.1.2 Secondary Objectives

The secondary objectives are:

- To assess toxicity and tolerability of the combination of nivolumab, ipilimumab and plinabulin.
- To measure the frequency of immune-related adverse events (irAEs). irAE's are defined as any treatment-related AE that is inflammatory in nature, consistent with the mechanism of action of immunotherapy and generally medically manageable with topical and/or systemic immunosuppressants.
- To determine the proportion of patients with a confirmed objective response in the 2 arms of the Phase II part (defined as the number of patients with a best overall response of complete response [CR] or PR divided by the number of assigned patients).
- To estimate clinical benefit rate (CBR: complete response, partial response, or stable disease).
- To estimate 6-month (±4 weeks) PFS.
- To estimate overall survival (OS) and 1-year OS.

2.1.3 Correlative/Exploratory Objectives

- To measure biomarkers of inflammation (high sensitivity C-reactive protein [hsCRP], erythrocyte sedimentation rate [ESR], serum amyloid A [SAA]) and haptoglobin.
- To correlate tumor mutational burden with PFS and ORR
- To measure biomarkers of activity such as immune cell phenotypes, TCR-seq, and circulating cytokines and to correlate with PFS and ORR.

2.2 Endpoints

2.2.1 Primary Endpoints

- Phase I: Grade 3 and 4 toxicities as defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.
- Phase II: PFS is defined as the time from D1 of treatment until the criteria for disease progression is met as defined by RECIST1.1 or death as a result of any cause.

2.2.2 Secondary Endpoints

- The objective response rate (ORR) is the proportion of all subjects with confirmed PR or CR according to RECIST 1.1, from the start of treatment until disease progression/recurrence.
- Overall survival is defined by the date of registration to date of death from any cause.
- Clinical Benefit Rate (CBR) is defined as the percentage of patients who achieve CR, PR and stable disease.

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

The patients must satisfy all of the following inclusion/exclusion criteria in order to be eligible for the study:

1. Must have signed and dated written informed consent form in accordance with regulatory and institutional guidelines.
2. Males and females aged >18 years at time of consent.
3. Histological or cytological confirmed extensive-stage SCLC
4. Patients who progressed after at least 1 platinum-based chemotherapy regimen. Patients with platinum resistance (defined as recurrence or progression of disease within 90 days of completion of the platinum-based regimen) are eligible. For phase II, patients also must have been treated with at least one prior line of PD-1/PD-L1 therapy.
5. Measurable disease according to RECIST v1.1 (Section 8) obtained by imaging within 28 days prior to study registration.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 within 14 days before registration and minimum life expectancy of at least 12 weeks.
7. Treatment to be initiated at least 2 weeks since last dose of prior systemic anticancer therapy (chemotherapy, radiation, and/or surgery.
8. Recovery to grade 1 of any clinically significant toxicity (excluding alopecia, grade 2 fatigue, vitiligo, endocrinopathies on stable replacement therapy) prior to initiation of study drugs.
9. Female patients of childbearing potential have a negative pregnancy test at baseline. Females of childbearing potential are defined as sexually mature women without prior hysterectomy or who have had any evidence of menses in the past 12 months. However, women who have been

amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, anti-estrogens, or ovarian suppression.

a. Women of childbearing potential (i.e., menstruating women) must have a negative urine pregnancy test (positive urine tests are to be confirmed by serum test) documented within 14 days of study registration and within the 24-hour period prior to the first dose of study drug.

b. Sexually active women of childbearing potential enrolled in the study must agree to use 2 forms of accepted methods of contraception during the course of the study and for 23 weeks after their last dose of study drug. Effective birth control includes (a) intrauterine device plus 1 barrier method; (b) on stable doses of hormonal contraception for at least 3 months (e.g., oral, injectable, implant, transdermal) plus one barrier method; (c) 2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm); or (d) a vasectomized partner.

c. For male patients who are sexually active and who are partners of premenopausal women: agreement to use 2 forms of contraception as in criterion 9b above during the treatment period and for 31 weeks after the last dose of study drug.

10. Adequate laboratory values.

a. Absolute neutrophil count ≥1,000/μL

b. Platelet count ≥100,000/μL

c. Hemoglobin ≥9.0 g/dL

d. Total bilirubin ≤1.5 x upper limit of normal (ULN) or ≤3 x ULN for subjects with Gilbert's disease

e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3.0 x ULN (≤5 x ULN if evidence of hepatic involvement by malignant disease)

f. Creatinine ≤ 1.5 x ULN or estimated glomerular filtration rate (eGFR) ≥40 mL/min/1.73m^2

g. Lipase and Amylase ≤1.5 x ULN. Subjects with Lipase >1.5 x ULN may enroll if there are neither clinical nor radiographic signs of a pancreatitis.

3.2 Exclusion Criteria

Patients with any of the following will be excluded from participation in the study.

1. Active interstitial lung disease (ILD) or pneumonitis or a history of ILD or pneumonitis requiring treatment with steroids. Prior history of radiation pneumonitis is allowed if pneumonitis was restricted to the field of radiation.
2. History of ileus or other significant gastrointestinal disorder known to increase the risk of ileus or chronic bowel hypomotility
3. Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 23 weeks (female) or 31 weeks (male) after the last dose of study drug.
4. Must not have received CTLA-4 targeted therapy previously

5. Treatment with any investigational agent within 28 days prior to registration for protocol therapy. Vaccination for SARS-CoV-2 is allowed as well as any therapy as required for the treatment of active COVID 19 infection.
6. Known active symptomatic central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with neurological symptoms must undergo a head computed tomography (CT) scan or brain magnetic resonance imaging (MRI) to exclude brain metastasis. Patients whose brain metastases have been treated may participate provided there is no evidence of progression for at least 2 weeks after CNS-directed treatment, as ascertained by clinical examination or brain imaging.
7. Known history of human immunodeficiency virus (HIV) or active hepatitis B (by surface antigen expression or polymerase chain reaction [PCR]) or active hepatitis C (by PCR) infection. NOTE: HIV testing is not required; Hepatitis B and C testing are required at screening.
8. Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to study registration.
9. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs) or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Vitiligo, alopecia, hypothyroidism only requiring hormone replacement, psoriasis not requiring systemic treatment, celiac disease controlled by diet alone or conditions not expected to recur in the absence of an external trigger are permitted.
10. A condition requiring systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to administration of study drugs.
11. History of psychiatric illness or social situations that would limit compliance with study requirements. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator.
12. Prior malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, melanoma, or breast) unless a complete remission was achieved at least 2 years prior to study entry.
13. Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association (NYHA) Class III–IV within 6 months prior to their first dose of study drugs.
14. Evidence of ongoing inadequately controlled hypertension (defined as baseline systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg).
15. Any active grade 3 or higher viral, bacterial, or fungal infection within 2 weeks of the first dose of the study drugs. Routine antimicrobial prophylaxis is permitted.

4. SUBJECT REGISTRATION

All subjects must be registered through Big Ten Cancer Research Consortium (Big Ten CRC) Administrative Headquarters'(AHQ) electronic data capture (EDC) system. A subject is considered registered when an 'On Study' date is entered into the EDC system.

Subjects must be registered prior to starting protocol therapy. Subjects must begin therapy within **5 business days** of registration.

5. STUDY DESIGN

5.1 Overview of Study Design

This is an open-label Phase I/II study, with a dose escalation part (Phase I) and a single-arm part (Phase II), in patients with recurrent SCLC who progressed after first-line platinum-based chemotherapy and who are candidates for second-line therapy.

No PK evaluation is planned in this study as nivolumab and ipilimumab are unlikely to alter plinabulin's PK, since the route of excretion is different.

5.2 Phase I (Dose Escalation)

The primary objective of the Phase I part of the study is to define the MTD of the triple combination of nivolumab, ipilimumab and plinabulin.

Dosing Regimen:

On Day 1 in a 21-day cycle, all patients will receive nivolumab (1 mg/kg, IV), ipilimumab (3 mg/kg, IV) and plinabulin (escalating cohorts, IV).

After 4 treatment cycles, ipilimumab will be discontinued and patients will continue treatment with nivolumab 240 mg and plinabulin every 2 weeks (maintenance period) until one of the end of treatment criteria occur.

Dose Escalation:

Dose escalation will follow a standard 3+3 design (Table 1). Patients will enter into cohorts of at least 3 evaluable patients starting with the initial plinabulin dose level at 20 mg/m^2 (Dose Level 1). If Dose Level 1 is deemed tolerable, the next cohort of patients will be enrolled into Dose Level 2 (plinabulin at 30 mg/m^2).

Table 1 Dose Escalation Schedule

Dose Level	Nivolumab Day 1 of each cycle	Ipilimumab Day 1 of each cycle	Plinabulin Day 1 of each cycle
Level -1	1 mg/kg	3 mg/kg	13.5 mg/m^2
Level 1 (start)	1 mg/kg	3 mg/kg	20 mg/m^2
Level 2	1 mg/kg	3 mg/kg	30 mg/m^2

In addition to the above dose levels, there are also 1 level below the initial level, in case the initial level has unacceptable toxicity.

The MTD is defined as the dose level at which fewer than 33% of subjects experience a dose limiting toxicity (DLT), and specifically is the dose level at which less than 2 out of 6 subjects experience DLT.

As no dose escalation is planned beyond level +2, if less than 2 out of 6 subjects experience DLT at level +2, MTD will be determined at this level (with no requirement for DLT at next higher dose level). The MTD will be the recommended dose for the Phase II component of the study.

Subjects will initially be enrolled onto dose level 1. Three to six evaluable subjects will be enrolled at each dose level. All subjects assigned to a dose level must be followed for at least 42 days (2 cycles) before dose escalation to the next cohort level can begin.

Note: Subjects not evaluable for DLT assessment (i.e. do not complete at least 2 cycles of therapy due to reasons other than toxicity) on the Phase I portion of the protocol will be replaced for determination of dose escalation.

The following rules will be followed:

- An initial three subjects will be enrolled at dose level +1. If all 3 subjects in dose level +1 complete 4 weeks of therapy without dose limiting toxicity (DLT), the study will proceed to enroll 3 subjects at dose level +2. If all 3 subjects in dose level +2 complete 2 cycles of therapy without DLT, 3 more subjects will be enrolled to ensure that only 0-1 of 6 subjects have a DLT and then proceed to the Phase II cohort. As dose level +2 represents the recommended phase II dose of plinabulin in single agent studies, there will be no further dose escalation beyond dose level +2.

- Alternatively, if 1 of the first 3 subjects in any given dose cohort experiences DLT, an additional 3 subjects will be enrolled at that dose level. If only 1 of the total 6 subjects in a dose level experience DLT, the study will proceed to the next dose level as planned. If 2 of the total 6 subjects in any given dose cohort experience DLT, the next lower dose level will be explored and considered the maximum tolerated dose (MTD) if no more than 1 of 6 subjects experience a DLT. That dose will be recommended for the Phase II study.

- If 2 or more DLTs are reached in dose level -1, the study will be put on hold and a protocol amendment will be considered.

Dose Escalation Rules

Number of subjects with DLT at given dose level	**Escalation decision**
0 out of 3	Enter 3 subjects at the next dose level.
≥2 out of 3	Dose escalation will be stopped. This dose level will be declared the **maximum administered dose**. Three (3) additional subjects will be entered at the next lower dose level if only 3 subjects were treated previously at that next lower dose level.
1 out of 3	Enter at least 3 more subjects at this dose level: • If 0 of these additional 3 subjects experience DLT, proceed to the next dose level. • If 1 or more of these additional 3 subjects experience DLT, then dose escalation is stopped and this dose is declared the

	maximum administered dose. Three (3) additional subjects will be entered at the next lower dose level if only 3 subjects were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximum administered dose	This will be defined as the MTD. This dose level will be the recommended Phase II dose.

5.3 Definition of Dose-Limiting Toxicity

Dose-limiting toxicities (DLTs) will be assessed for each patient within 42 days of first plinabulin dose. Any suspected or confirmed DLT should be reported immediately (within 1 business day) to Big Ten CRC Administrative Headquarters.

DLTs will be counted based on the number of subjects with DLT at a given dose level, not the absolute number of DLTs. No single subject can trigger more than one DLT event.

Intra-subject dose escalation is not permitted.

A DLT is defined as any of the following treatment-related AEs or laboratory abnormalities, graded according to NCI CTCAE version 4:

- Febrile neutropenia
- Grade 4 hypertension
- Grade 4 anemia unrelated to underlying disease
- Grade 3 thrombocytopenia with clinically significant bleeding or grade 4 thrombocytopenia lasting more than 7 days and/or requiring a platelet transfusion
- Grade 4 neutropenia lasting more than 7 days
- ≥Grade 3 nausea, vomiting, diarrhea, or electrolyte imbalances lasting >48 hours despite optimal prophylactic and curative treatment
- ≥Grade 3 hypersensitivity reaction (unless first occurrence and resolves within 6 hours with appropriate clinical management)
- Treatment delay >21 days secondary to recovery from study drugs-related AEs.
- ≥Grade 3 non-hematologic AEs, except for the exclusions listed below.
- Any toxicity requiring permanent discontinuation of treatment, including:
  - Grade ≥3 diarrhea
  - Grade ≥3 adrenal insufficiency
  - Grade 4 hyperglycemia

The following events will be excluded from the DLT definition:

- Any AE ≥grade 3 clearly determined to be unrelated to study drug(s) (e.g., disease progression)
- ≥Grade 3 isolated alkaline phosphatase laboratory abnormality of any duration
- ≥Grade 3 isolated, asymptomatic amylase or lipase laboratory abnormality of any duration
- ≥Grade 3 endocrinopathies controlled by corticosteroids or hormone replacement
- Vitiligo or Alopecia of any grade
- Grade 3 fatigue.

In order to be evaluable for DLT assessment, patients must receive a complete dose of nivolumab, ipilimumab and plinabulin. Patients who experience a DLT within the first 42 days of treatment and drop out of the study will be considered evaluable for DLT and will not be replaced. Patients who drop out of the study for reasons other than DLT will be considered not evaluable and will be replaced.

5.4 Phase II

The primary objective of the Phase II part of the study is to determine if the addition of plinabulin to double checkpoint inhibition (PD-1 and CTLA-4) for recurrent SCLC will improve PFS. Phase II will begin after the R2PD of plinabulin is identified for use in combination with nivolumab and ipilimumab.

The RP2D of plinabulin is 30 mg/m^2.

6. TREATMENT PLAN

Study treatment will be administered as 21-day cycles for the first 4 cycles and as 14-day cycles during the maintenance period.

For patients with a body surface area (BSA) greater than 2.4 m^2, dosing should be calculated using a maximum BSA of 2.4 m^2 for plinabulin.

6.1 Phase I (Dose Escalation)

6.1.1 Cycles 1 to 4 (cycle = 21 days)

Patients will be treated in cohorts of at least 3 patients. On Day 1 of each 21-day cycle, all patients will receive treatment with:

- First: Nivolumab 1 mg/kg administered via IV infusion over 30 minutes (-5/+10 minutes)
- Second: Ipilimumab 3 mg/kg administered via IV infusion over 30 minutes (-5/+10 minutes)
- Third: Plinabulin administered via IV infusion over 60 minutes (-5/+10 minutes) beginning 1 hour (± 10 minutes) after the end of the ipilimumab infusion.

6.1.2 Cycle 5 and Subsequent Cycles (Maintenance) (cycle = 14 days)

After 4 treatment cycles, ipilimumab will be discontinued and patients will continue treatment with nivolumab 240 mg and plinabulin every 2 weeks (maintenance period) until one of the end of treatment criteria occur.

On Day 1 of each 14-day cycle, all patients will receive treatment with:

- First: Nivolumab 240 mg administered via IV infusion over 30 minutes (-5/+10 minutes)
- Second: Plinabulin administered via IV infusion over 60 minutes (-5/+10 minutes) beginning 30 minutes (± 5 minutes) after the end of the nivolumab infusion.

6.2 Phase II

Up to 26 patients will enrolled to receive the triple combination of plinabulin + nivolumab + ipilimumab.

6.2.1 Cycles 1 to 4 (cycle = 21 days)

Patients will receive study treatment via IV infusion on Day 1 in a 21-day cycle:

- First: Nivolumab 1 mg/kg administered via IV infusion over 30 minutes(-5/+10 minutes)
- Second: Ipilimumab 3 mg/kg administered via IV infusion over 30 minutes(-5/+10 minutes)
- Third: Plinabulin at RP2D administered via IV infusion over 90 minutes (-5/+10 minutes) beginning 1 hour (± 10 minutes) after the end of the ipilimumab infusion. Plinabulin can be administered over 60 minutes cycle 3 onwards if patient does not experience an infusion reaction with the first two cycles.

6.2.2 Cycle 5 and Subsequent Cycles (Maintenance) (cycle = 14 days)

After 4 treatment cycles, ipilimumab will be discontinued and patients will continue treatment with nivolumab 240 mg and plinabulin every 2 weeks (maintenance period) until one of the end of treatment criteria occur.

On Day 1 of each 14-day cycle, patients will receive treatment with:

- First: Nivolumab 240 mg administered via IV infusion over 30 minutes (-5/+10 minutes)
- Second: Plinabulin administered via IV infusion over 60 minutes (-5/+10 minutes) beginning 30 minutes (± 5 minutes) after the end of the nivolumab infusion.

6.3 Vital Signs During Plinabulin Infusions

Vital signs (temperature, blood pressure, heart rate, and respiratory rate) should be measured immediately before and after (±10 min) plinabulin infusions, and 30 and 60 minutes following (±10 minutes) plinabulin infusion during Cycle 1 Day 1. Thereafter, vital signs will be collected immediately before and after each infusion (±10 min). Abnormal vital signs (especially hypertension) should be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant, whichever occurs first.

6.4 Allowed Concomitant Medications

If an increase in systolic blood pressure to >160 mmHg is observed after administration of plinabulin, oral amlodipine 10 mg or an equivalent calcium channel blocker should be administered before each subsequent dose. Increases in systolic blood pressure above 200 mmHg should be managed with nitroprusside or similar regimen per institutional practice. If hypertension can be successfully managed, the patient can continue in the study at the discretion of the treating Investigator.

The Investigator should be experienced in the use of nivolumab and ipilumumab and familiar with the prescribing information provided by the manufacturer. According to the prescribing information, there have been no formal clinical studies to evaluate the drug interactions of either nivolumab or ipilumumab with other medications.

Any other medication which is considered necessary for the patient's welfare, including bisphosphonates, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the Investigator. Vaccination for SARS-CoV-2 as well as any therapy as required for the treatment for active COVID 19 infection is allowed. However, vaccination is not recommended on the day of IP administration.

All medications will be recorded in an appropriate section of the CRF.

No other cancer therapies or investigational agents are permitted during the entire duration of the study treatment (from 14 days before the first administration until the 30-day safety evaluation).

6.5 Supportive Care

Plinabulin is associated with the occurrence of nausea, vomiting and diarrhea. These GI-related AEs are dose-dependent and occur primarily at the 30 mg/m^2 plinabulin dose, and if infused over 30 minutes. With infusion time of 60 minutes, the frequency of these GI-related AEs is markedly reduced. A 60-minute infusion time is implemented in this protocol. Nevertheless, if GI-related AEs occur after the first plinabulin dosing, consider administering anti-emetic prophylaxis with subsequent plinabulin dosing.

Appropriate anti-emetic prophylaxis (excluding steroids) should be given per institutional policy prior to plinabulin infusion to prevent nausea or vomiting. Suggested regimen includes a 5HT3 antagonist such as palonosetron. The use of anti-emetics must be recorded on the eCRF.

If diarrhea occurs, it must be treated. Anti-diarrheals such as loperamide (or diphenoxylate/atropine) must be prescribed for diarrhea. Suggested loperamide use: 4 mg orally after first loose stool, then 2 mg after each stool not to exceed 16 mg in 24 hours. Anti-diarrheal medications must be recorded on the eCRF.

Milk and milk products should be avoided, and other appropriate dietary interventions should be advised to patients. Patients should also be cautioned to avoid dehydration, and of the importance to drink water and electrolyte containing fluids throughout the day when diarrhea occurs. If IV fluids are needed, their administration must be recorded on the eCRF.

Prophylaxis with bowel motility agents should follow institutional practice as applied to drugs such as vincristine, including the use of agents such as stool softeners, bulking agents, stimulating agents and/or dopamine antagonists. The use of opiates should be limited to when clearly indicated and prophylaxis for opiate induced constipation with agents such as methylnaltrexone should be administered. If significant constipation develops, it should be managed immediately and plinabulin administration should be delayed until resolution. Careful observance for signs of ileus and early diagnostic evaluation with radiographic and/or ultrasound studies is recommended.

6.5.1 Suggested supportive care measures for the management of adverse events that are related to nivolumab or ipilimumab

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered immuno-oncology agents in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of AEs: Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathies, Skin, Neurological.

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an AE, consider recommendations provided in the algorithms. These algorithms are found in Appendix 1. The guidance provided in these algorithms should not replace the Investigator's medical judgment but should complement it.

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.

Patients who are started on steroids for management of an immune-related event should not resume immunotherapy until steroids have been tapered to ≤ prednisone 10mg daily or an equivalent dose of an alternative corticosteroid.

- **Management of Infusion Reactions:** Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs.

  The table below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of nivolumab.

Management of Infusion Related Reaction (IRR), Allergic Reaction, Hypersensitivity reaction or Bronchospasm from Nivolumab or Ipilimumab

Description	Action
CTCAE Grade 1 IRR, allergic reaction or bronchospasm[1]	Remain at bedside and monitor subject until recovery from symptoms.
CTCAE Grade 2 IRR, allergic reaction or bronchospasm[1]	Stop the infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).
CTCAE Grade 3 or 4 IRR, allergic reaction, bronchospasm or hypersensitivity reaction[2]	Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will

	not recur. ***Nivolumab or ipilimumab will be permanently discontinued***. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).
[1]For any ≤Grade 2 IRR, allergic reaction or bronchospasm, see Section 5.1.2 for recommended premedication for subsequent infusions. [2]Hypersensitivity reactions included in CTCAEv4 include anaphylaxis, Stevens-Johnson syndrome and toxic epidermal necrolysis; in the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).	

7. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v4 will be used to grade adverse events. Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

7.1 Dose Delays/Dose Modifications

In the event of multiple toxicities, dose delays and modifications should occur in accordance with the highest grade of AEs observed.

All patients with evidence of radiographically confirmed progressive disease or clinical evidence of disease progression or global deterioration of health unrelated to progressive disease, as defined by RECIST version 1.1, will be discontinued from study treatment.

7.1.1 Criteria for Treatment

In the absence of disease progression, laboratory tests are required prior to Day 1 of each cycle as per the schedule of assessments. The follow criteria must be met:

- AST ≤ 3 ULN, ALT ≤ 3 ULN (≤ 1.5 x ULN if alkaline phosphatase is > 2.5 x ULN)
- Serum bilirubin ≤ 1.5 x ULN (unless patient has Gilbert's disease, then bilirubin ≤ 3.0 x ULN)
- Creatinine ≤ 1.5 x ULN
- Hemoglobin ≥ 9 g/dL
- Absolute neutrophil count ≥ 1.0 x 10^9/L
- Platelets ≥ 100 x 10^9/L

7.1.2 Plinabulin

The dose levels and the general approach to dose delay and modification of plinabulin are shown below. Plinabulin dosing must be withheld if the patient has evidence or signs of any medical condition that would prevent dosing (such as an infection, grade 4 neutropenia, or unacceptable medical condition).

At the discretion of the Investigator, the dose may be delayed for up to 6 weeks for any toxicity possibly or probably related to plinabulin that does not meet DLT criteria. Dosage interruptions to assess or treat intercurrent illnesses are allowed and should be clearly described in the study eCRF. A delay greater than 6 weeks will require the patient to be removed from the study (except in case of potential patient benefit, which must be approved by the Sponsor Investigator).

Table 3 Plinabulin Dose Delay and Modification Guidelines

Adverse Reaction	Provide Supportive Care for:	Withhold Plinabulin For:	Permanently Discontinue Plinabulin For:
Infusion related reaction	**Grade 2**: Stop the infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, restart the infusion at 50% of the original infusion rate when symptoms resolve. Monitor subject closely. If symptoms recur, then no further plinabulin will be administered at that visit. Administer diphenhydramine 50 mg IV, remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). Consider premedicating with dexamethasone 2 to 4 mg daily on days -1, 1, 2 of treatment for subsequent cycles.		Grade 3 or 4: Immediately discontinue infusion of plinabulin Begin an IV infusion of normal saline and treat the subject as follows. • Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).
Cytokine release syndrome	Management of symptoms such as fever and muscle pain with acetaminophen or other analgesic. Consider oxygen therapy, fluids and antihypotensive agents (if hypotensive) for grade 2 or higher. For grade 2 symptoms that do not resolve or for grade 3 or higher symptoms, high-dose steroids should be initiated and patient should be admitted for management and observation.	**Grade 2:** May restart plinabulin at one dose level lower once symptoms resolve.	**Grade 3 or 4**
Hyperten-sion	**For BP > 160**: oral amlodipine 10 mg or an equivalent calcium channel blocker should be administered before each subsequent dose. Increases	• First occurrence of BP > 140 and <160 with the use of anti-hypertensives.	• Second occurrence of BP >140 and <160 with use of antihypertensive and one dose reduction

Adverse Reaction	Provide Supportive Care for:	Withhold Plinabulin For:	Permanently Discontinue Plinabulin For:
	in systolic blood pressure above 200 mmHg should be managed with nitroprusside or similar regimen per institutional practice	• May restart plinabulin at one dose level lower with anti-hypertensive prophylaxis once BP returns to grade 1 or better	**OR** First occurrence of BP ≥ 160in spite of anti-hypertensives.
Diarrhea	Grade 1 or 2 diarrhea. Institute symptomatic treatment including hydration, electrolyte replacement, dietary changes, and loperamide or other per institutional guidelines.	• First occurrence of grade 3 event. Withhold plinabulin and institute symptomatic treatment. Plinabulin may be restarted at the same dose level once toxicity resolved to grade 1 or better if SYMPTOMATIC treatment controlled diarrhea. • Grade 3 event in patients on optimal symptomatic treatment: Withhold plinabulin and restart at one dose level lower once event resolves to grade 1 or better.	• Any grade 4 event. • Recurrence of grade 3 diarrhea after one dose reduction and optimal symptomatic treatment

Table 4 Plinabulin Dose Reduction Levels

Dose Level	Plinabulin dose
-1	13.5 mg/m^2
1	20 mg/m^2
2	30 mg/m^2

7.1.3 Nivolumab and Ipilimumab

Treatment with nivolumab and ipilimumab will be held for:

- Drug-related grade 4 hematological toxicities
- ≥Grade 3 non-hematological toxicity (except for fatigue, alopecia and vitiligo OR isolated laboratory abnormalities with no clinical correlate)
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator (in consultation with the study monitor), warrants delaying the dose of study medication
- In the event of isolated CNS progression during study treatment, study drug(s) may be withheld while palliative treatment is administered, e.g. a standard course of whole brain radiotherapy in accordance with institutional practice, and restarted within 1 week after completion of radiotherapy. During this time the patient should be fully evaluated for other sites of disease progression. If treatment is delayed >6 weeks, the patient must be permanently discontinued from all study therapy, except as specified in Dose Discontinuation Criteria.
- If guidelines for an irAE are not specified in Table 4 below, nivolumab and ipilumumab should be held for any ≥grade 3 irAE, and can be resumed if the irAE recovers to grade 0-1. Systemic corticosteroids (1-2 mg/kg/day) are indicated for all grade 3 or 4 irAEs if not otherwise specified. Steroids should be tapered once symptoms improve to grade 1 or less and tapered over at least 1 month.

If an irAE is suspected, a thorough evaluation should be conducted in an effort to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to diagnosing an irAE. Serological, immunological and histological (biopsy) data should be considered to support the diagnosis of an immune-related toxicity. All irAEs are graded according to CTCAE, version 4.

Nivolumab and ipilumumab will be permanently discontinued for:

- Grade ≥3 diarrhea or colitis
- Grade ≥3 adrenal insufficiency
- Life-threatening or grade 4 AE
- Any severe or grade 3 treatment-related AE that recurs
- Inability to reduce corticosteroid dose to ≤10 mg of prednisolone or equivalent/day within 6 weeks
- Persistent grade 2 or 3 treatment-related adverse reactions that do not recover to grade 1 or resolve within 6 weeks after last dose.

Table 5 Nivolumab/Ipilumumab Dose Modifications Guidelines

Adverse Reaction	Withhold Nivolumab/Ipilimumab For:	Permanently Discontinue Nivolumab/Ipilimumab For:
Pneumonitis	Grade 2 • Promptly initiate empiric steroids (prednisone 1-2 mg/kg/day or equivalent) • If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. If still no improvement within 3-5 days, promptly start immunosuppressive therapy such as TNF inhibitors (e.g. infliximab). • Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and in particular, anti PCP treatment	Grade 3 or 4 • Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent • Hospitalize the patient, obtain pulmonary consult, supportive care (oxygen etc.) • If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g. infliximab) • Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and in particular, anti PCP treatment
Hepatitis	≥ Grade 2 if patient has baseline AST, ALT or total bilirubin that is within normal limits • Regular checking of LFTs (e.g. every 1-2 days) until elevations of these are improving or resolved. • If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2 mg/kg/day or IV equivalent. • If still no improvement within 3-5 days, consider additional workup and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. • If still no improvement within 3-5 days despite 2-4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil). Infliximab should NOT be used. • Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment	AST or ALT > 8 x ULN OR total bilirubin >5 x ULN OR concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN Any grade 4 • Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent • If still no improvement within 3-5 days, promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Infliximab should NOT be used. • Hepatology consult, abdominal workup, and imaging as appropriate. • Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment
Diarrhea/Colitis	Grade 2	Grade 3 or 4

Adverse Reaction	Withhold Nivolumab/Ipilimumab For:	Permanently Discontinue Nivolumab/Ipilimumab For:
	• Symptomatic treatment including hydration, electrolyte replacement, dietary changes, and loperamide and/or budesonide. Consider hospitalization if grade 3. • Promptly start prednisone 1 to 2 mg/kg/day or IV equivalent • If event is not responsive within 3-5 days or worsens, GI consult should be obtained for further workup such as imaging and/or colonoscopy, and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. • If still no improvement within 3-5 days despite 2-4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab. Caution: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab • Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment	• Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent • Hospitalize patient, urgent GI consult and imaging and/or colonoscopy as appropriate • If still no improvement within 3-5 days, promptly start further immunosuppressives (e.g. infliximab). Caution: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. • Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment
Nephritis and renal dysfunction	Grade 2 • Carefully monitor serum creatinine every 2-3 days and as clinically warranted • Consult Nephrologist and consider renal biopsy if clinically indicated • If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day or IV equivalent • If event is not responsive within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4 mg/kg/day started. • Once improving gradually taper steroids over ≥28 days and consider	Grade 3 or 4 • Carefully monitor serum creatinine every 1-2 days • Consult Nephrologist and consider renal biopsy if clinically indicated • Promptly start prednisone 1 to 2 mg/kg/day or IV equivalent • If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. • Once improving, gradually taper steroids over ≥28 days and consider

Adverse Reaction	Withhold Nivolumab/Ipilimumab For:	Permanently Discontinue Nivolumab/Ipilimumab For:
	prophylactic antibiotics, antifungals and anti PCP treatment	prophylactic antibiotics, antifungals and anti PCP treatment
Rash (excluding Bullous skin formations) **IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED AND STUDY DRUG DISCONTINUED**	Grade 2 or 3 • Obtain dermatology consult • Symptomatic topical treatment • Consider moderate-strength topical steroid • If no improvement of rash/skin lesions within 3-5 days or is worsening, promptly start systemic steroids prednisone 1-2 mg/kg/day or IV equivalent • Consider skin biopsy if persistent for >1-2 weeks or recurs • Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment	Grade 4 • Hospitalize patient and consult dermatology • Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent • Consider skin biopsy • Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment
Type I diabetes mellitus [TIDM] (if new onset) or Hyperglycemia	Grade 2 or 3 • Obtain endocrinology consult • Consider short term corticosteroids or hormone replacement therapy as indicated • If no improvement within 3-5 days or is worsening, promptly start systemic steroids prednisone 1-2 mg/kg/day or IV equivalent • Consider hospitalization if grade 3 • Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment	Grade 4 • Hospitalize patient and consult endocrinology • Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent • Administer hormone replacement therapy as indicated • Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment
Hypophysitis	Grade 2 or 3 • Obtain endocrinology consult • Consider short term corticosteroids or hormone replacement therapy as indicated • If no improvement within 3-5 days or is worsening, promptly start systemic	Grade 4 • Hospitalize patient and consult endocrinology • Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent • Administer hormone replacement therapy as indicated

Adverse Reaction	Withhold Nivolumab/Ipilimumab For:	Permanently Discontinue Nivolumab/Ipilimumab For:
	steroids prednisone 1-2 mg/kg/day or IV equivalent • Consider hospitalization if grade 3 • Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment	• Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment
Adrenal insufficiency	Grade 2 • Obtain endocrinology consult • Consider short term corticosteroids or hormone replacement therapy as indicated • If no improvement within 3-5 days or is worsening, promptly start systemic steroids prednisone 1-2 mg/kg/day or IV equivalent • Consider hospitalization if grade 3 • Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment	Grade 3 or 4 • Hospitalize patient and consult endocrinology • Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent • Administer hormone replacement therapy as indicated • Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment
Immune mediated Neurotoxicity	Grade 2 • Discuss with the study physician • Obtain Neurology Consult • Pain medications as indicated • Promptly start systemic steroids prednisone 1-2mg/kg/day or IV equivalent • If no improvement within 3-5 days despite 1-2 mg/kg/day prednisone or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (e.g. IVIG)	Grade 3 or 4 • Discuss with study physician • Hospitalize and obtain Neurology Consult • Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent • If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IVIG) • Once stable, gradually taper steroids over ≥4 weeks
Uveitis	≥ Grade 2 • - Obtain ophthalmology consult • - Promptly initiate topical steroids • - If no improvement within 3-5 days or is worsening, promptly start systemic	≥ Grade 2 (if not improving to grade 1 within 2 weeks while receiving topical treatment OR requiring systemic treatment)

Adverse Reaction	Withhold Nivolumab/Ipilimumab For:	Permanently Discontinue Nivolumab/Ipilimumab For:
	steroids prednisone 1-2 mg/kg/day or IV equivalent • - Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment	

There are no dose recommendations for hypothyroidism or hyperthyroidism. Isolated grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to <grade 4 within 1 week of onset do not require treatment modifications. If the decision is made to resume dosing, the patient should restart treatment on the next regularly scheduled dosing visit. Skipped doses are not to be replaced.

Patients should receive appropriate supportive care measures as deemed necessary by the Investigator. For further recommendations, see the "Immune Mediated Adverse Reaction Management Guide" (Bristol-Myers Squibb 2017).

7.2 Protocol Discontinuation

If a subject decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete the final study assessments. The site study team should contact the subject by telephone or through a clinic visit to determine the reason for the study withdrawal. If the reason for withdrawal is an adverse event, it will be recorded on the eCRF.

8. CALENDAR & EVALUATIONS

	Screen	Cycle = 21 days[2]		Cycle = 14 days[2]	Safety follow up	Long-term Follow up
		Cycle 1	Cycles 2-4	Cycle 5+		
	-28 days[1]	D1	D1	D1	30 days post Tx	Q 3 months (±14 days)
REQUIRED ASSESSMENTS						
Informed Consent	X					
Medical history, smoking history, trial awareness, prior NGS[16]	X					
Diagnosis and Staging[3]	X					
AEs (esp. constipation) & Concomitant Medications[4]	X	X	X	X	+30,+100	
PE, VS, ECOG PS, weight, height (screen only)[5]	X	X	X	X	X	
Electrocardiogram	X				X	
LABORATORY ASSESSMENTS						
Complete Blood Count, Chemistry[6]	X	X	X	X	X	
LDH, Lipase, Amylase[6]	X	X	X	X	X	
PT, PTT, INR	X					
Hepatitis B and C testing[7]	X					
ACTH, TSH, T3/T4[8]	X	X	X	Every odd cycle	X	
Urinalysis	X					
Pregnancy test WOCBP[9]	-14 d	X	X	X		
DISEASE ASSESSMENT						
Disease Imaging[10]	X		post C2, C4	Q4 cycles		
TREATMENT EXPOSURE						
Nivolumab: 1 mg/kg		X	X			
Nivolumab: 240 mg flat dose				X		
Ipilimumab: 3 mg/kg		X	X			
Plinabulin[11]: PhI escalating cohorts; Ph II 30 mg/m^2		X[5]	X[5]	X[5]		
CORRELATIVE STUDIES (SPECIMEN COLLECTION)						
Whole blood for hsCRP, ESR, SAA; haptoglobin & cytokine levels (Ph.II only)[12]		X	X	X	X	
Whole Blood for PBMCs and Plasma[13]		X	C3D1		X	
BANKING SAMPLES (SPECIMEN COLLECTION)						
Whole Blood, Serum and Plasma[14]		X		C5D1	X	
Unstained Slides[15]	X				Bx@PD	
FOLLOW-UP						
Survival status, subsequent therapy						X

Key to Footnotes

1. Screening (baseline) labs performed within 7 days of C1D1 treatment do not need to be repeated.
2. A window of ±3 days will be applied to all treatment visits; a window of ±7 days will apply for all safety follow-up visits and tumor imaging.
3. Diagnosis and staging to include pathology report and Tumor Node Metastasis (TNM) staging
4. AEs and Conmeds: Patients should specifically be asked about signs of constipation and treatment provided when indicated. A safety follow-up visit will occur 30 days (±7 days) after the last dose of treatment. An additional assessment of AEs will be performed 100 days (±14 days) after last dose of study drugs. Patients with drug related AEs of ≥grade 2 observed at the 30-day safety assessment, should be followed-up monthly during clinical visits until the AE has resolved to grade 1, the event is believed to be chronic, or patient receives other anti-cancer therapy, whichever occurs first. Concomitant medications are to be recorded up to the 30-day Safety Visit. Concomitant medications should only be recorded after the safety visit if it relates to an unresolved AE.
5. Physical Exam (PE), Vital Signs (VS), ECOG Performance Status (PS), weight, and height (screening only). Vital signs include: temperature, blood pressure, heart rate, and respiratory rate. Vital signs should be measured immediately before, after (±10 min), and 30 and 60 minutes following the plinabulin infusion on Cycle 1 Day 1. Thereafter, vital signs are collected immediately before and after each infusion.
6. **CBC to include**: hemoglobin, hematocrit, red blood cell and white blood cell counts with differential and platelets. CBC may be monitored on a more frequent basis, in accordance with institutional guidelines, should a patient have grade 4 hematologic AEs. **Chemistry to include**: sodium, potassium, bicarbonate, chloride, bicarbonate, calcium, magnesium, glucose, urea Nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total protein, albumin, lipase, amylase, and total bilirubin (plus direct bilirubin if total bilirubin is elevated).
7. Hepatitis B and C tests include hepatitis B surface antigen, antibody to the hepatitis B core antigen, and hepatitis C virus antibody. Results that may be consistent with chronic or active infection must be confirmed by PCR tests for hepatitis B and/or C.
8. Adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), and triiodothyronine (T3) and/or free thyroxine (free T4); free or total T3/T4 will be performed as per local standards.
9. Women of childbearing potential must have a negative urine pregnancy test within 14 days of study registration and within 24-hours prior to each plinabulin infusion. Positive urine tests should be confirmed with a serum test.
10. Perform CT scan of the abdomen/pelvis, CT of the chest, or additional staging as required for each patient. A bone scan will only be performed in patients with known bone metastasis at study entry to monitor the status of metastatic disease in bone. Target and non-target lesion response and overall disease response are to be assessed (RECIST 1.1) after cycle 2 and after cycle 4. After that, assess every 4 cycles (post C8, C12, etc.). End of treatment tumor assessment will be done at the discretion of the treating physician.
11. Plinabulin will be administered 60 minutes after end of ipilimumab infusion (Cycles 1 to 4) or 30 minutes after end of nivolumab infusion (maintenance period). Vital signs will be assessed as per footnote #5.
12. Mandatory whole blood for high sensitivity C-reactive protein [hsCRP], erythrocyte sedimentation rate [ESR], serum amyloid A [SAA]. Phase II only: Mandatory whole blood for haptoglobin and cytokine levels in addition to the labs above for Ph 2 subjects on D1 of every cycle.
13. Mandatory whole blood for PBMCs and plasma for banking to be collected pre-Treatment C1D1, C3D1, and at safety follow up. See CLM for collection, processing, labeling, and shipping instructions.
14. Optional whole blood, serum and plasma for banking are to be collected at Pre-Treatment Cycle 1 Day 1, pre-treatment Cycle 5 Day 1, and at 30-day safety follow up visit. See CLM for collection, processing, labeling and shipping instructions.
15. Optional submission of unstained slides for banking from an archived FFPE tumor block or fresh biopsy. At disease progression, an optional tumor biopsy may be performed and tumor sample stored for banking. See CLM for collection, labeling, and shipping instructions.
16. Prior NGS/genetic testing results for tumor mutational burden are requested, if available.

8.1 Study Assessments and Procedures

Informed consent must be obtained before any study-specific samples are taken or study-specific tests or evaluations are conducted. Screening/baseline assessments should be performed within 28 days of study registration. Study eligibility will be based on satisfying all of the study inclusion and exclusion criteria. The patient's cancer diagnosis including prior treatment and the patient's demographics will be documented. Test results performed as part of standard of care within the required time frame may be used in lieu of repeating the tests required for eligibility.

8.1.1 Laboratory and Other Assessments

1. **Hematology:** Hemoglobin, hematocrit, red blood cell count (RBC), white blood cell count (WBC) with differential, and platelet count will be obtained for all treatment cycles. WBC (including differential) outside of normal range can be retested to determine eligibility. Complete blood count (CBC) will be monitored on a more frequent basis, in accordance with institutional guidelines, should a patient have grade 4 hematological AEs. Results of all baseline tests must be reviewed for eligibility by the treating Investigator or their designee prior to registration. In addition, results of hemoglobin, absolute neutrophil count, and platelet count must be reviewed prior to each infusion.
2. **Blood chemistry/electrolytes:** Sodium, potassium, chloride, bicarbonate, calcium, magnesium, glucose, BUN, serum creatinine, ALT, AST, alkaline phosphatase, LDH, total protein, albumin, lipase, amylase, and total bilirubin (plus direct bilirubin if total bilirubin is elevated).

   Results of all baseline tests must be reviewed for eligibility by the treating Investigator or their designee prior to registration. Results of AST, ALT, AP, bilirubin, and creatinine must be reviewed prior to each infusion.
3. **Pregnancy test:** Urine dipstick pregnancy tests are to be performed for females of childbearing potential at each treatment visit. Positive urine tests are to be confirmed with serum pregnancy testing.
4. **Urinalysis**: Glucose, blood, protein and pH. If blood or protein in urine is present, a microscopic examination is required. Results of all baseline tests must be reviewed for eligibility by the treating Investigator or their designee prior to registration.
5. **Endocrine tests**: Including adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), and T3 and/or T4 (free or total will be performed as per local standards).

8.1.2 Prior and Concomitant Medications

All concomitant medications will be recorded from the time the patient signs the informed consent form until discontinuation of treatment. Concomitant medications will only be collected after treatment discontinuation if it is associated with an on ongoing AE.

8.2 Screening Visit and Baseline (Within 28 Days Prior to Registration)

At the screening visit, information will be collected and patients will have clinical evaluations as follows:

- Informed consent

- Medical history (including events up until treatment); demographics; smoking history; trial awareness question; prior NGS/genetic testing
- Diagnosis and staging
- Tumor assessments and measurement
- Concomitant medications (starting from the time the patient signs the informed consent)
- Complete physical examination, including height (screen only) and weight
- Vital sign measurements
- ECOG Performance status;
- Baseline electrocardiogram (ECG)
- Hematology, serum chemistry and urinalysis, endocrine labs, coagulation tests, Hepatitis B and C tests
- Inflammation serum biomarkers
- Urine pregnancy test, if applicable (positive results to be confirmed by serum pregnancy testing)
- Unstained slides:
  - For banking (with subject consent)

8.3 On Treatment Evaluations

8.3.1 Day 1 of Each Cycle

- Concomitant medications
- Physical examination
- Vital sign measurements
- ECOG Performance status
- Hematology, serum chemistry,
- Endocrine labs (every odd cycle after first 4 cycles)
- Inflammation serum biomarkers
- Urine pregnancy test, if applicable (positive results to be confirmed by serum pregnancy testing)
- Nivolumab infusion
- Ipilimumab infusion (Cycles 1-4 only)
- Plinabulin infusion
- AEs. Patients should specifically be asked about signs of constipation and treatment provided when indicated.
- Whole blood for hsCRP, ESR, SAA (mandatory). Ph 2: haptoglobin and cytokine levels.
- Cycle 1 and Cycle 3 only: Whole blood for PBMC (mandatory) and plasma isolation for banking (with subject consent)
- Cycle 1 and 5 only: Whole blood, serum and plasma for banking (with subject consent)

8.3.2 Post Cycle 2, Cycle 4 and Every 4 Cycles Thereafter

- Disease assessment after cycle 2 and after cycle 4. After that, assessments will be done every 4 cycles (post C8, C12, etc.).

8.4 Protocol Discontinuation and Assessment

In addition to discontinuation from treatment related toxicities as described in Section 7, a subject will also be discontinued from protocol therapy and followed up per protocol under the circumstances

outlined below. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF).

- Documented disease progression
- The treating physician thinks a change of therapy would be in the best interest of the subject
- The subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
    - If a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- A female subject becomes pregnant
- If plinabulin or nivolumab is interrupted for ≥ 6 weeks.

All patients who have received at least 1 dose of study drug and have discontinued treatment for any reason will have an 30-day Safety assessment performed.

The Safety Follow up assessments should include the following:

- Concomitant medications
- Complete physical examination, including weight
- Vital signs measurements
- ECOG Performance Status
- Electrocardiogram (ECG)
- Hematology, serum chemistry, endocrine labs
- Inflammation serum biomarkers
- AEs
- Disease assessment should be done at the discretion of the treating physician.
- Whole blood for hsCRP, ESR, SAA (mandatory). Ph 2: haptoglobin and cytokine levels.
- Whole blood for PBMC (mandatory) and plasma isolation for banking (with subject consent)
- Whole blood, serum and plasma for banking (with subject consent)
- Optional biopsy: At disease progression, tumor biopsy may be performed and tumor sample stored for banking.

An additional assessment of AEs will be performed 100 days (±14 days) after last dose of study drugs.

8.5 Surgery or Radiation Therapy

Treatment of isolated/symptomatic lesions by local surgery or radiation therapy is permitted for palliative or potentially curative management at any time beyond Cycle 2. Radiation should not be given within 7 days prior to plinabulin administration. Surgery should be performed after holding plinabulin for 21 days and can be resumed 21 days after surgery. All interventions must be discussed in advance with the Sponsor Investigator.

8.5.1 Adverse Event Assessments

Information regarding the occurrence of SAEs will be collected from the time the patient signs the informed consent form. AEs will be collected after registration. SAEs and AEs will be collected throughout their participation in the study, including a period of 100 days after the patient's last active dose of study drug, unless a new treatment has been started. SAEs that occurs more than 100 days after

the last dose of study drug need not be reported unless the Investigator considers them related to study drug.

8.6 Safety Follow-up Evaluations

For the purpose of this study, all AEs irrespective of causality will be collected from registration. A safety follow-up visit should occur when subjects permanently stop study treatment for whatever reason (toxicity, progression, or at discretion of site investigator) and should be performed 30 days and 100 days (±7 days) after the last dose of treatment. Subjects who have an ongoing ≥ grade 2 or serious AE (SAE) at this visit will continue to be followed until the AE resolves to ≤ Grade 1 or baseline, is deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier.

8.7 Long Term Follow-up Evaluations

All patients (phase I and phase II) will be followed at least every 3 months (±7 days) for survival for up to one year following their Safety Follow up visit, unless the trial is completed or terminated or informed consent is withdrawn. Follow up will continue even if the patient receives another anticancer therapy. Patients can consent to participate in follow-up assessments even if consent for study participation has been withdrawn.

If patient discontinues study therapy for a reason other than progression, disease assessment will continue until disease progression is found or the patient initiates next treatment, whichever occurs first.

Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate.

9. BIOSPECIMEN STUDIES AND PROCEDURES

9.1 Biomarkers of Inflammation and Cytokine Panels

Levels of (high sensitivity C-reactive protein [hsCRP], erythrocyte sedimentation rate [ESR], serum amyloid A [SAA]) in whole blood will be measured on day 1 of each cycle and at the Safety Follow up visit for all subjects. In addition, phase 2 subjects will also have blood drawn for haptoglobin analysis and cytokine levels. Haptoglobin and cytokine levels in whole blood will be measured on day 1 of each cycle and at the Safety Follow up visit.

The following cytokine and chemokine panels will be considered, but other cytokine and/or chemokine panels may be considered in the future:

- Proinflammatory panel: 10plex (IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, and TNF-α
- Cytokine panel: 10plex (GM-CSF, IL-1α, IL-5, IL-7, IL-12/IL-23p40, IL-15, IL-16, IL-17A, TNF-β, and VEGF-A)
- Chemokine panel: Eotaxin, Eotaxin-3, IL-8, IL-8 (HA), IP-10, MCP-1, MCP-4, MDC, MIP-1α, MIP-1β, TARC
- CCL5 (RANTES): single chemokine analysis

All of these analyses will be done at LabCorp (formerly known as Covance laboratories). Refer to the CLM for collection, processing, labeling and shipping instructions.

9.2 Tumor Mutation burden

The tumor mutational burden will be correlated with PFS and ORR. Tumor mutation burden will be measured using next generation sequencing based on in vitro diagnostic tests. Prior NGS/genetic testing results (if available) will be requested at the time of patient enrollment on study. Information about the main cancer-related gene alterations from the next gen sequencing results will also be collected for exploratory purposes.

9.3 Immunophenotyping/Immune Repertoire TCR Sequencing

Whole blood for PBMCs and plasma isolation will be collected at pre-treatment C1D1, C3D1, and at the safety follow up visit and shipped overnight for processing. PBMCs will be cryopreserved prior to analysis. Cryopreserved PBMCs will be used for immunophenotyping by flow cytometry and immune repertoire TCR sequencing.

9.4 Banking of Leftover Biospecimens

Subject consent will be obtained to bank any leftover samples that were collected for study-specific correlative research. Hoosier Cancer Research Network (HCRN), as Administrative Headquarters for the Big Ten CRC, will manage the banked samples. Samples will be banked indefinitely in the Hoosier Cancer Research Network Biorepository and used for future unspecified cancer-related research.

9.5 Samples for future unspecified studies

Subject consent will be obtained to collect additional samples for future unspecified Big Ten Cancer Research Consortium studies. Hoosier Cancer Research Network, as Administrative Headquarters for the Big Ten CRC, will manage the banked samples. Samples will be banked indefinitely in the Hoosier Cancer Research Network Biorepository.

This includes:

- Whole blood: Whole blood will be collected prior to treatment on Cycle 1 Day 1, Cycle 5 Day 1 and at 30-day safety follow up visit.
- Pre- and Post-treatment plasma: Whole blood for plasma will be collected prior to treatment on Cycle 1 Day 1, Cycle 5 Day 1 and at the 30-day Safety Follow-up visit.
- Pre- and Post-treatment serum: Whole blood for serum will be collected prior to treatment on Cycle 1 Day 1, Cycle 5 Day 1 and at the 30-day Safety Follow-up visit.
- Unstained slides: Unstained slides will be obtained from the subject's archived formalin fixed paraffin embedded tumor sample or fresh biopsy. At disease progression, an optional tumor biopsy may be performed and tumor sample stored for banking.

Please refer to the Correlative Laboratory Manual (CLM) for all sample collection, processing, labeling, and shipping instructions.

9.6 Confidentiality of Biospecimens

Samples will be identified by a subject's study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

10. CRITERIA FOR DISEASE EVALUATION

For the purposes of this study, all tumor assessments must be completed following the same methodology as used for the screening assessment. Methodology and disease response will be assessed as specified in RECIST 1.1 guidelines. During study treatment, disease status will be assessed after cycle 2 and after cycle 4. After that, assess every 4 cycles (post C8, C12, etc.). Perform CT scan of the abdomen/pelvis, CT of the chest, or additional staging as required for each patient. A bone scan will only be performed in patients with known bone metastasis at study entry to monitor the status of metastatic disease in bone. If radiologic imaging shows progressive disease (PD), tumor assessment may be repeated approximately 4-6 weeks later in order to confirm continued PD (as compared to the initial scan). Treatment may continue at the discretion of the treating physician while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction or stabilization in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued as per treatment calendar.

10.1 Measurable Disease

Measurable disease is defined as the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

10.1.1 Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

10.2 Non-measurable Lesions

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

NOTE: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

10.3 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If

lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

10.4 Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

10.5 Evaluation of Target Lesions

NOTE: In addition to the information below, also see section 4.3.2 in the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

10.6 Evaluation of Non-target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not

	normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor investigator.

10.7 Evaluation of Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/ or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Non-evaluable
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

11. DRUG INFORMATION

11.1 Plinabulin

The clinical formulation of plinabulin will be supplied as a clear, yellow/orange solution in amber vials containing 40mg of drug in 10mL or 80 mg of drug in 20 mL (4 mg/mL).

11.1.1 Drug Administration

The calculated dose (mg) of plinabulin (at a concentration of 4 mg/mL in the vial) is diluted in dextrose 5% in water (D5W) and administered IV with an in-line filter peripherally or centrally. The diluted dose must be used within 6 hours of dilution. Plinabulin must be protected from light at all times (storage, prior to, during and after dilution). Instructions for pharmacy drug preparation can be found in the study Pharmacy Manual. The plinabulin dose should be calculated based on the baseline BSA, as described in Section 6. If BSA subsequently varies from baseline by more than ±10%, then the newer BSA value should be used for calculation of subsequent doses.

11.1.2 Storage and Stability

Plinabulin must be stored at room temperature and protected from light. Each vial is designated for single use. Vials should be stored upright.

11.1.3 Source of Drug

Plinabulin is an investigational drug that will be supplied by BeyondSpring Pharmaceuticals, Inc. at no charge to subjects participating in this clinical trial.

11.1.4 Product Accountability

The designated pharmacist will acknowledge receipt of the drug shipment and note content and condition of the package and vials on the clinical material shipping form. Refer to the Pharmacy Manual for further information.

All expired or unused medication will be destroyed on site according to site procedures. Big Ten CRC will be notified prior to destruction.

The pharmacist or person responsible for dispensing the study drug at the site will maintain an accurate and current record of all drug supplies received and dispensed to study patients. See Documents/Info tab of the EDC for sample dispensing record.

11.1.5 Adverse Events

Two clinical studies with plinabulin have been conducted to date, a Phase I monotherapy study and a Phase I/II combination study with docetaxel in NSCLC. A total of 141 patients with advanced cancer received plinabulin.

In the Phase I monotherapy study (NPI-2358-100), plinabulin was generally well tolerated. AEs occurring in ≥ 20% of patients included nausea (61%), vomiting (47%), diarrhea and fatigue (34% respectively), constipation, pyrexia, and headache (26% respectively), anorexia (24%), and anemia (21%). Overall, 16 patients (42%) experienced serious adverse events (SAEs), the majority were considered not related to plinabulin.

In the Phase I/II combination study with docetaxel, plinabulin was also found to be generally well tolerated. The combination appeared to have a similar AE profile as single-agent docetaxel. In patients receiving plinabulin/docetaxel (DN) at 30 mg/m^2 of plinabulin (RP2D), the most common AEs regardless of causality were diarrhea (58%), fatigue (52%), nausea (48%), constipation (36%), vomiting (34%), anorexia (34%), and hypertension (32%). Unexpectedly, a significantly lower rate of neutropenia (all events and events ≥ Grade 3) was observed in patients in DN arm than in docetaxel (D) arm

(p≤0.01). The use of G-CSF and the rate of docetaxel dose reduction were also lower in DN than in D arm.

11.2 Nivolumab (Opdivo®)

11.2.1 Supplier/How Supplied

Bristol-Meyers Squibb will supply nivolumab at no charge to subjects participating in this clinical trial.

The site investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

11.2.2 Product Description and Dosage Form

Nivolumab, available in the United States as Opdivo, is a sterile, preservative-free, nonpyrogenic, clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles. Opdivo injection for IV infusion is supplied in single-dose vials. It is supplied in single-use vials of 100 mg, 10 mg/mL. Each mL of Opdivo solution contains nivolumab 10 mg, mannitol (30 mg), pentetic acid (0.008 mg), polysorbate 80 (0.2 mg), sodium chloride (2.92 mg), sodium citrate dihydrate (5.88 mg), and Water for Injection, USP. May contain hydrochloric acid and/or sodium hydroxide to adjust pH to 6 (BMS, 2016). Additional details or updates may be found in the most recent Prescribing Information.

11.2.3 Storage and Stability

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Store nivolumab under refrigeration at 2°C to 8°C (36°F to 46°F). Protect nivolumab from light by storing in the original package until time of use. Do not freeze or shake. For additional details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the BMS-936558 (nivolumab) Investigator Brochure section for “Recommended Storage and Use Conditions.”

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

11.2.4 Handling and Disposal

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis. Please refer to the Investigator Brochure for nivolumab handling instructions.

After final drug reconciliation, unused nivolumab vials should be disposed at the site following procedures for the disposal of anticancer drugs.

11.2.5 Dispensing

Nivolumab must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Clinical supplies may not be used for any purpose other than that

stated in the protocol. The site investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

11.2.6 Administration

Nivolumab is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding polyethersulfone membrane in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyvinyl chloride (PVC) and non-PVC/non-DEHP (di(2-ethylhexyl)phthalate) containers/IV components or glass bottles have been observed.

11.2.7 Adverse Events

Please refer to the nivolumab Investigator's Brochure for a complete list of adverse events.

Potential safety concerns and recommended management guidelines regarding pulmonary toxicities, GI toxicities, hepatotoxicities, endocrinopathies, dermatologic toxicities, and other toxicities of concern are summarized below. Management algorithms are found in Appendix 1.

The overall safety experience with nivolumab is based on experience as either monotherapy or in combination with other therapeutics. In general, for monotherapy, the safety profile is similar across tumor types. The only exception is pulmonary inflammation AEs, which may be numerically greater in subjects with NSCLC, possibly because in some cases, it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes.

Most common adverse reactions (≥20%) in patients were:

- Nivolumab as a single agent: fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia, headache, abdominal pain.
- Nivolumab with ipilimumab for melanoma: fatigue, rash, diarrhea, nausea, pyrexia, vomiting, and dyspnea.
- Nivolumab with ipilimumab for renal cell carcinoma: fatigue, rash, diarrhea, musculoskeletal pain, pruritus, nausea, cough, pyrexia, arthralgia and decreased appetite.

11.3 Ipilimumab (Yervoy™)

11.3.1 Supplier/How Supplied

Bristol-Meyers Squibb will supply ipilimumab at no charge to subjects participating in this clinical trial.

The site investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

11.3.2 Product Description and Dosage Form

Ipilimumab, available in the United States as Yervoy, is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for IV infusion, which may contain a small amount of visible translucent-to-white, amorphous ipilimumab particulates. It is supplied in single-use vials of 200 mg/40 mL. Each milliliter contains 5 mg of ipilimumab and the following inactive ingredients: diethylene triamine pentaacetic acid (DTPA) (0.04 mg), mannitol (10 mg), polysorbate 80 (vegetable origin) (0.1 mg), sodium chloride (5.85 mg), tris hydrochloride (3.15 mg), and Water for Injection, USP at a pH of 7 (BMS 2015).

11.3.3 Storage and Stability

Ipilimumab Injection, 200 mg/40 mL (5 mg/mL), must be stored refrigerated (2°C to 8°C) and protected from light. Ipilimumab injection must not be frozen. Partially used vials or empty vials of ipilimumab injection should be discarded at the site according to appropriate drug disposal procedures.

Ipilimumab injection may be stored undiluted (5 mg/mL) or following dilution in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection in PVC, non-PVC/non-DEHP or glass containers for up to 24 hours (at 2°C to 8°C) or RT/RL.

Recommended safety measures for preparation and handling include protective clothing, gloves, and safety cabinets.

11.3.4 Handling and Disposal

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis. Please refer to the Investigator Brochure for ipilimumab handling instructions.

After final drug reconciliation, unused ipilimumab vials should be disposed at the site following procedures for the disposal of anticancer drugs.

11.3.5 Dispensing

Ipilimumab must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Clinical supplies may not be used for any purpose other than that stated in the protocol. The site investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

11.3.6 Adverse Events

Please refer to the ipilimumab Investigator's Brochure or prescribing information for a complete list of adverse events.

Blockade of CTLA-4 by ipilimumab leads to T-cell activation, with the potential for clinical inflammatory AEs primarily involving the skin (dermatitis/pruritus), GI tract (diarrhea/colitis), liver (hepatitis), endocrine glands (eg, hypophysitis and adrenal or thyroid abnormalities), and other less frequent organs (eg, uveitis/episcleritis). The majority of these inflammatory AEs initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab.

The majority of the inflammatory AEs is reversible with the guidance issued in Appendix 1. In rare cases, these inflammatory AEs may be fatal.

The most common adverse reactions (≥5%) are fatigue, diarrhea, pruritus, rash, and colitis. Additional common adverse reactions at the 10 mg/kg dose (≥5%) include nausea, vomiting, headache, weight loss, pyrexia, decreased appetite, and insomnia.

12. ADVERSE EVENTS

12.1 Definitions

12.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

12.1.2 Immune-related Adverse Events (irAEs)

irAE's are defined as any treatment-related AE that is inflammatory in nature, is consistent with the mechanism of action of immunotherapy and generally medically manageable with topical and/or systemic immunosuppressants.

12.1.3 Serious Adverse Event (SAE)

An SAE is an adverse event that:

- Results in death.
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect

- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

12.1.4 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, package insert, or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

12.1.5 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	The Adverse Event is ***not related*** to the drug(s)
Unlikely	The Adverse Event is ***doubtfully related*** to the drug(s)
Possible	The Adverse Event ***may be related*** to the drug(s)
Probable	The Adverse Event is ***likely related*** to the drug(s)
Definite	The Adverse Event is ***clearly related*** to the drug(s)

12.2 Reporting

12.2.1 Adverse Events and Immune Related Adverse Events

- AEs and irAEs will be recorded from time of registration until 100 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- AEs will be recorded whether or not they are considered related to the study drug(s).
- All AEs/ irAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- Asymptomatic laboratory abnormalities that do not require treatment will not be collected as adverse events.
- All patients experiencing SAE/AEs or serious irAEs/ irAEs resulting in permanent discontinuation from the study regardless of seriousness or relationship to study drug or experiencing treatment-related toxicities of grade ≥2 at the End of Treatment visit should be followed-up monthly until all the toxicities are resolved to grade ≤1, or stabilized, or patient receives other anti-cancer therapy, whichever occurs first.

12.2.2 Serious Adverse Events (SAEs)

12.2.2.1 Site Requirements for Reporting SAEs to Big Ten CRC Administrative Headquarters

- SAEs/ serious irAEs will be reported from time of registration until 100 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- SAEs/ serious irAEs will be reported on the SAE Submission Form and entered in the SAE tab in the EDC system **within 1 business day** of discovery of the event.
- SAEs include events related and unrelated to the study drug(s).
- All SAEs/ serious irAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All SAEs regardless of relation to study drug and serious irAEs will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.

The site will submit the completed SAE Submission Form (see Documents/Info tab of the EDC) to Big Ten CRC AHQ within **1 business day** of discovery of the event. The form will be sent electronically to Big Ten CRC AHQ at SAFETY@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies of the SAE as per local requirements.

The original copy of the SAE Submission Form and the email correspondence or fax confirmation sheet must be kept within the study file at the study site.

If an ongoing SAE changes in intensity or causal relationship to the investigational product, or if new information becomes available, a follow-up SAE report should be sent electronically to Big Ten CRC AHQ at SAFETY@hoosiercancer.org within 1 business day. Once the SAE has resolved, sites must submit a follow up SAE Submission Form within a reasonable timeframe to Big Ten CRC AHQ at SAFETY@hoosiercancer.org.

12.3 Site Requirements for Reporting Pregnancy to Big Ten CRC Administrative Headquarters

A female patient of childbearing potential must be instructed to immediately inform the Investigator if she becomes pregnant during the study. Pregnancies occurring up to 23 weeks after the completion of treatment with plinabulin must also be reported to the Investigator. The Investigator should counsel the patient; discuss the risks of continuing with the pregnancy and the possible effects on the fetus (congenital anomalies). Monitoring of the patient will continue until conclusion of the pregnancy. Patients who become pregnant while on study will be discontinued from the study treatment and all safety follow up procedures will be performed.

Pregnancy occurring up to 31 weeks after the completion of plinabulin in the partner of a patient participating in the study should also be immediately reported to the Investigator and the Sponsor. The partner should be counseled and followed as described above. Pregnant partners of male participants will also be followed until the conclusion of the pregnancy.

Pregnancy is not an SAE. However, the outcome of a pregnancy must be reported to detect a potential SAE (congenital anomaly, premature birth, or birth defect). All pregnancies must be initially reported and follow-up information must be provided on the pregnancy form. The timeframe to report a

pregnancy to Big Ten CRC AHQ is from start of study drug up to 23 weeks (female) or 31 weeks (male) after the last dose of study drug. If the outcome of the pregnancy meets any SAE criterion (including stillbirth, neonatal death, spontaneous abortion, or congenital anomaly – including that in an aborted fetus) the Investigator must follow the procedures for reporting SAEs. Any neonatal death occurring ≤30 days after birth will be reported as an SAE. If a pregnancy occurs in the female partner of a male patient, the Investigator will then (and only then) also be required to obtain her consent to hold her data on file. If the female partner is unwilling to sign the consent, her data may not be held in the safety database. However, this will not affect the ability of the male patient to continue in the study.

12.3.1.1 Big Ten CRC AHQ Requirements for Reporting SAEs to BeyondSpring Pharmaceuticals

Big Ten CRC AHQ will report SAEs to Beyond Spring Pharmaceuticals within **1 business day** of receipt of the SAE Reporting Form from a site. Follow-up information will be provided to Beyond Spring Pharmaceuticals as it is received from a site.

Contact information for sending SAE information to BeyondSpring Pharmaceuticals:

SAE Email Address: ICON-Safety-CentralReceipt@iconplc.com
SAE Facsimile Number (when e-mail is offline): 215-616-3096

12.3.1.2 Big Ten CRC AHQ Requirements for Reporting SAEs to Bristol Myers-Squibb

Big Ten CRC AHQ will report all SAEs to Bristol Myers-Squibb within **1 business day** of receipt of the SAE Reporting Form from a site. Follow-up information will be provided to Bristol Myers-Squibb as it is received from a site.

Contact information for sending SAE information to BMS:

SAE Email Address: Worldwide.Safety@BMS.com
SAE Facsimile Number: 609-818-3804

12.3.1.3 Sponsor-Investigator Responsibilities

Big Ten CRC AHQ will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

12.3.1.4 Big Ten CRC AHQ Responsibilities for Reporting SAEs to FDA

Big Ten CRC AHQ has been designated to manage the Investigational New Drug Application (IND) associated with this protocol on behalf of the sponsor-investigator. Big Ten CRC AHQ will cross-reference this submission to Beyond Spring Pharmaceuticals's parent IND at the time of submission. Additionally, Big Ten CRC AHQ will submit a copy of these documents to Beyond Spring Pharmaceuticals at the time of submission to FDA.

Big Ten CRC AHQ will be responsible for all communication with the FDA in accordance with 21CFR312 which includes but is not limited to the 7 and 15 Day Reports, as well as an Annual Progress Report. Additionally, Big Ten CRC AHQ will submit a copy of these reports to Beyond Spring Pharmaceuticals at the time of submission to FDA.

12.3.1.5 IND Safety Reports Unrelated to this Trial

Beyond Spring Pharmaceuticals will provide Big Ten CRC AHQ with IND safety reports from external studies that involve the study drug(s) per their guidelines. Big Ten CRC AHQ will forward the safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. Big Ten CRC AHQ will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via the EDC system.

Upon receipt from Big Ten CRC AHQ, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

13. STATISTICAL METHODS

13.1 Study Design

This is an open-label Phase I/II study, with a dose escalation part (Phase I) and a single arm part (Phase II), in patients with recurrent SCLC who progressed after first-line platinum-based chemotherapy and who are candidates for second-line therapy.

13.2 Endpoints

13.2.1 Definition of Primary Endpoint

- The safety endpoints for Phase I are the incidence of grade 3 and 4 toxicities as defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v4
- PFS in the Phase II part of the study

13.2.2 Definition of Secondary Endpoints

- ORR in the Phase II part of the study.
- CBR: complete response, partial response, or stable disease.
- 6-month PFS.
- OS and 1-year OS.

13.3 Sample Size and Accrual

For the Phase I part of the study, between 9 and 15 patients will be enrolled over a period of 6-9 months.

For the Phase II portion of the study, there will be one treatment arm with a total of 26 patients. Patients who receive plinabulin at RP2D level in phase I dose-escalation will count towards the 26 patients. The RP2D for plinabulin is 30 mg/m^2. Accrual will be over 18 months.

Patients in the phase I part who withdraw from the study before the last day of Cycle 2, for reasons other than DLT, will be replaced. The replacement patient will be dosed at the same dose level as the patient who withdrew.

For the Phase II portion of the study, there will be one treatment arm, and PFS will be the primary outcome. In previous studies, without plinabulin, the median survival was 1.5 months (Ready et al 2020). It is anticipated to be able to detect, with 80% power, an increase in PFS from 1.5 to 3.5 months (a 2 month increase), with a two-sided 5% level test of survival. Assuming an accrual period of 12 months and an additional 1 year of follow-up time, this increase could be detected by accruing 26 patients. Patients who receive plinabulin at RP2D level in phase I dose-escalation will count towards the 26 patients and will be included in the efficacy analysis.

13.4 Analysis Populations

Safety Population: all patients who receive at least 1 cycle or have at least 1 post-dose safety assessment.

DLT Evaluable Population: all patients in the dose-escalation part who receive 2 cycles of nivolumab, ipilimumab and plinabulin. Patients who experience a DLT within the first 42 days of treatment and drop out of the study will be considered evaluable for DLT and will not be replaced. Patients who drop out of the study for reasons other than DLT will be considered not evaluable and will be replaced.

Efficacy Evaluable Population: all patients who receive RP2D of plinabulin and meet the following 2 criteria will be considered evaluable for efficacy:

- patients who receive at least 2 cycles of therapy
- patients who have at least 1 on-study disease assessment or who expire prior to the first planned on-study disease assessment.

13.5 Assessment of Safety

13.5.1 Adverse Events

All treatment emergent AEs will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4, and grouped by the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term and System Organ Class, and summarized by worst grade severity per patient.

Treatment emergent AEs are those events that occur after first administration of any study therapy through 100 days post last dose of any active study therapy, and/or any treatment-related AEs, regardless of the onset date.

13.5.2 Deaths

Treatment emergent deaths are those deaths within 30 days of last dose of any study therapy. Early deaths are those deaths within 60 days of the first dose of study therapy.

Treatment emergent and/or early deaths will be tabulated and summarized by treatment groups.

13.5.3 Other Serious Adverse Events

SAEs are those events that result in death, are life-threatening, require or prolong inpatient hospitalization, result in persistent or significant disability/incapacity, or result in a congenital anomaly or birth defect in the fetus of a study patient pregnancy.

All treatment emergent SAEs will be tabulated and summarized by MedDRA preferred term and treatment groups.

13.5.4 Other Significant Adverse Events

All treatment emergent AEs leading to withdrawal of study therapy will be tabulated and summarized by CTCAE v4.0 MedDRA preferred term and treatment groups.

13.6 Data Analysis Plans

13.6.1 Analysis Plans for Primary Objective

Progression-free Survival (PFS)
PFS is time from registration to the first documented tumor progression, or death due to any cause whichever occurred first. PFS time of any living patient with no documented progression, or any patient starting other cytotoxic and/or cytostatic therapies, will be censored at the date of last evaluable disease assessment on-study. PFS time of patients with no evaluable disease assessment on-study will be censored at registration.

Distributions of PFS times will be estimated using the Kaplan-Meier product-limit method. The median PFS times with two-sided 95% CIs will be estimated. In addition, Royston-Parmar models will be used to visualize the hazard rate functions and the survival functions (Royston and Parmar 2002, Lambert and Royston 2009). For the definition of disease progression, refer to RECIST version 1.1.

13.6.2 Analysis Plans for Secondary Objectives

Overall Survival (OS): OS time is from registration to death due to any cause. OS time of living patients will be censored at the date last known alive. Distributions of OS times will be estimated using the Kaplan-Meier product-limit method. The median OS times with two-sided 95% confidence intervals (CIs) will be estimated. In addition, Royston-Parmar models will be used to visualize the hazard rate functions and the survival functions (Royston and Parmar 2002, Lambert and Royston 2009).

Objective Response Rate (ORR): ORR to protocol treatment will be evaluated by RECIST version 1.1, and the best overall response will be classified as complete response (CR), partial response (PR), stable disease, progressive disease (PD), and not evaluable (NE). ORR is defined as the proportion of patients with a best overall response of CR or PR, divided by the number of assigned patients.

Clinical Benefit Rate (CBR): CBR is defined as the percentage of patients who achieve CR, PR and stable disease.

13.7 Analysis Plans for Correlative/ Exploratory Objectives

13.7.1 Biomarkers of Inflammation

Levels of high sensitivity C-reactive protein [hsCRP], erythrocyte sedimentation rate [ESR], serum amyloid A [SAA] and haptoglobin will be measured in whole blood on day 1 of each cycle. Changes over time in the levels of these biomarkers will be measured using paired t-tests. Univariate analysis using logistic regression will be utilized to assess for an association between plinabulin use and levels of each of these markers.

13.7.2 Tumor Mutation Burden

Tumor mutation burden (TMB) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB will be measured in mutations per megabase (mb). TMB levels will be divided into three groups: low (1-5 mutations/mb), intermediate (6-19 mutations/mb), and high (≥ 20 mutations/mb). For analyses, comparisons will be made between both low to intermediate vs. high and low vs. intermediate to high TMB. Correlations between TMB and (1) PFS and (2) ORR, will be calculated using Spearman correlation formula. Linear regressions will also be performed using the least squares method.

13.8 Interim Analysis/Criteria for Stopping Study

For an early and detailed safety assessment, complete review of the AE data for the first 9 patients treated with plinabulin/nivolumab/ipilimumab will occur after completion of 2 cycles (6 weeks) of therapy. The toxicity rate (for grade 3 and 4 treatment-related events) has been observed to be around 30% with prior studies (Antonia et al 2016). If 3 or more patients experience 1 or more grade 3 or 4 treatment-related AE, further enrollment will stop until detailed analysis of the AE data occurs.

14. TRIAL MANAGEMENT

14.1 Data and Safety Monitoring Plan (DSMP)

The study will be conducted in accordance with Rutgers Cancer Institute of New Jersey Comprehensive Cancer Center DSMP.

Big Ten CRC AHQ oversight activities include:

- Review all adverse events requiring expedited reporting as defined in the protocol
- Notify participating sites of adverse events requiring expedited reporting
- Provide trial accrual progress, safety information, and data summary reports to the sponsor-investigator
- Submit data summary reports to the lead institution Data Safety Monitoring Committee for review as per their DSMP

14.2 Rutgers Cancer Institute of New Jersey Data Safety Monitoring Committee

The Rutgers CINJ DSMC will review the following:

- Adverse event summary report
- Audit results, if applicable
- Data related to stopping/decision rules described in study design
- Study accrual patterns
- Protocol deviations

The Rutgers CINJ DSMC will review study data every quarter. Documentation of DSMC reviews will be provided to sponsor-investigator and Big Ten CRC AHQ. Issues of immediate concern by the DSMC will be brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate. The sponsor-investigator will work with Big Ten CRC AHQ to address the DSMC's concerns.

14.3 Data Quality Oversight Activities

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel.

Monitoring visits to the trial sites may be made periodically during the trial to ensure key aspects of the protocol are followed. Additional for-cause visits may occur as necessary. Source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by Big Ten CRC AHQ or its designee.

The trial site may also be subject to quality assurance audit by BeyondSpring, Bristol Myers-Squibb or their designees as well as inspection by appropriate regulatory agencies.

14.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to Big Ten CRC AHQ for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

14.5 Protocol and/or Informed Consent Amendments

Modification to the protocol or the Informed consent must be made only after consultation between an appropriate representative of the Big Ten CRC Administrative Headquarters and the Sponsor Investigator. Protocol Amendments must be drafted by Big Ten CRC Administrative Headquarters and initially reviewed and approved by the Sponsor Investigator.

Once the Sponsor Investigator has approved the protocol amendment, the document must be submitted to the appropriate Independent Ethics Committee or Institutional Review Board for review and approval in accordance with institutional and Regulatory agency. IRB approval must be received in writing before any protocol changes can be implemented, except for changes necessary to eliminate an immediate hazard to study patients.

15. DATA HANDLING AND RECORD KEEPING

15.1 Data Management

Big Ten CRC AHQ will serve as the Clinical Research Organization for this trial. Data will be collected through a web-based clinical research platform compliant with Good Clinical Practices and Federal Rules and Regulations. Big Ten CRC AHQ personnel will coordinate and manage data for quality

control assurance and integrity. All data will be collected and entered into the EDC system by study site personnel from participating institutions.

15.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in the EDC system or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives. Please see the Data and Safety Oversight Process (DSOP) guidelines for further details.

The completed dataset is housed at Big Ten CRC AHQ and is the sole property of the sponsor-investigator's institution. It should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the sponsor-investigator and Big Ten CRC AHQ. After the initial publication, the complete data set will be available to all Big Ten CRC institutions.

15.3 Record Retention

To enable evaluations and/or audits from Health Authorities/Big Ten CRC AHQ, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with local and federal regulations. No records will be destroyed until Big Ten CRC AHQ confirms destruction is permitted.

15.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, Big Ten CRC AHQ, BeyondSpring, Bristol Myers-Squibb, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subjects's identity will remain confidential.

16. ETHICS

16.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to Big Ten CRC AHQ before he or she can enroll subjects into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB as local regulations require.

Progress reports and notifications of adverse events will be provided to the IRB according to local regulations and guidelines.

16.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

16.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

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18. APPENDIX 1: ADVERSE EVENT MANAGEMENT ALGORITHMS

These general guidelines constitute guidance to the site Investigator and may be supplemented through discussions with the Sponsor-Investigator by contacting the Big Ten CRC project manager. The guidance applies to all immuno-oncology agents and regimens.

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

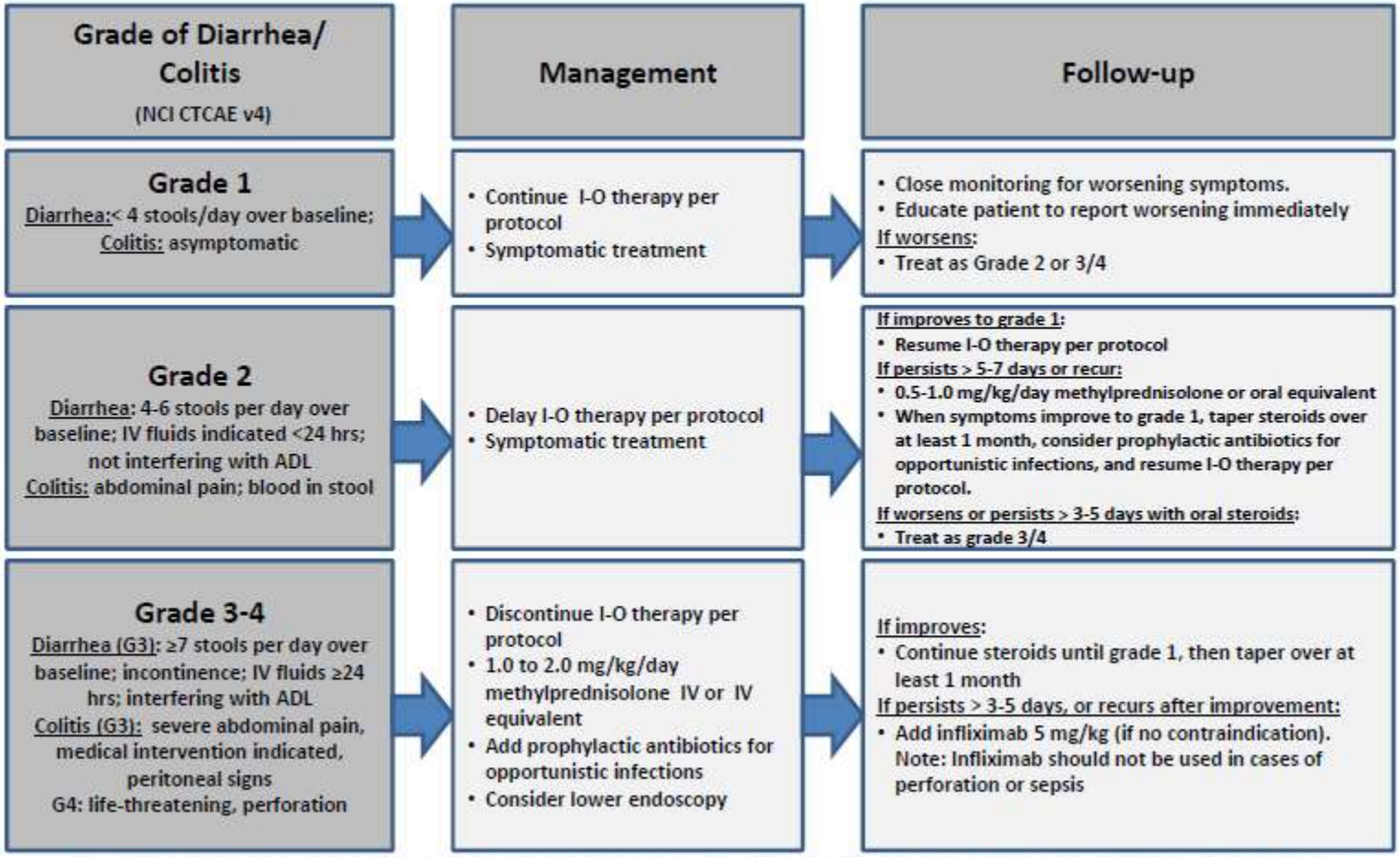
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

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

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.

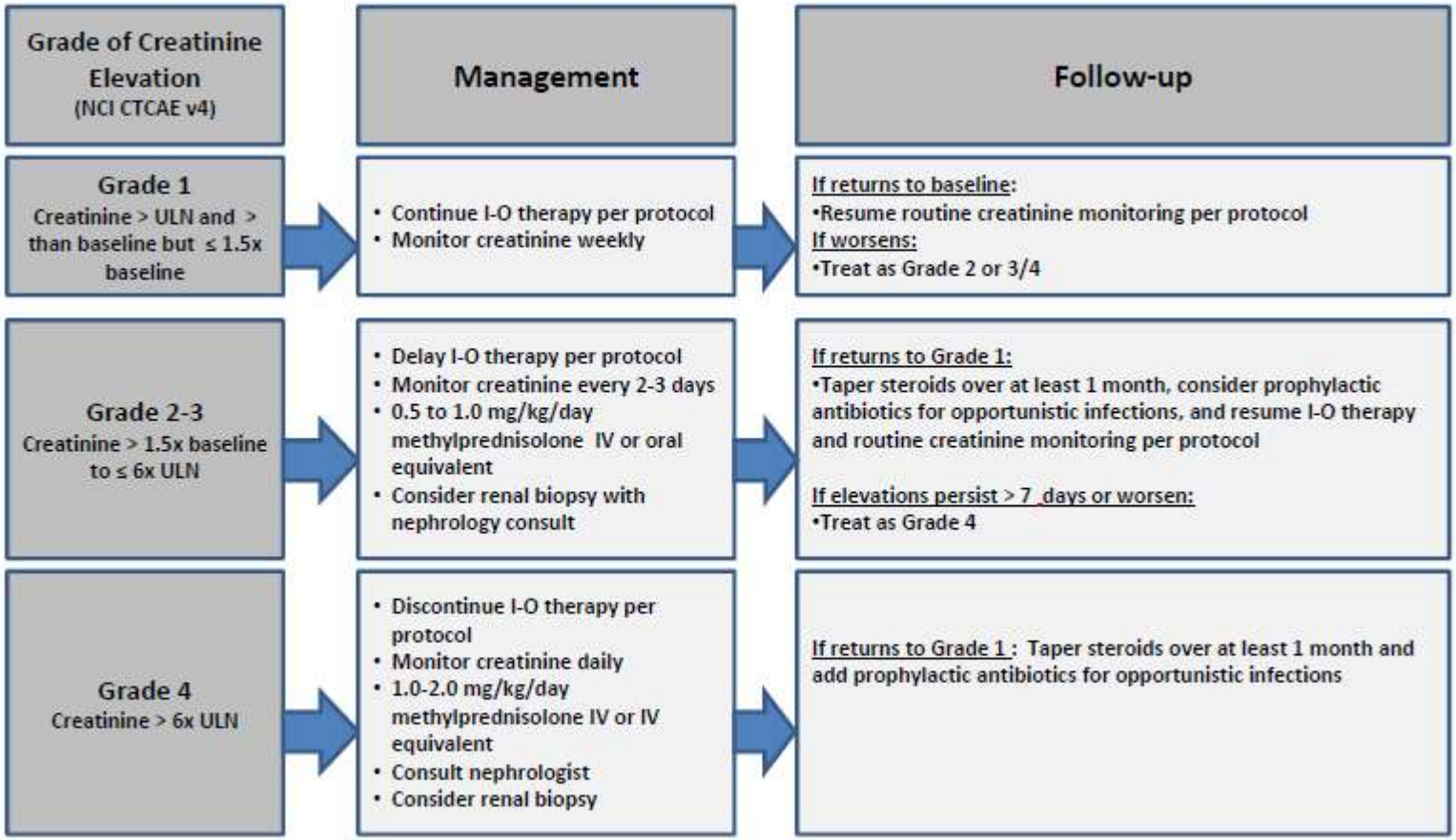


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

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

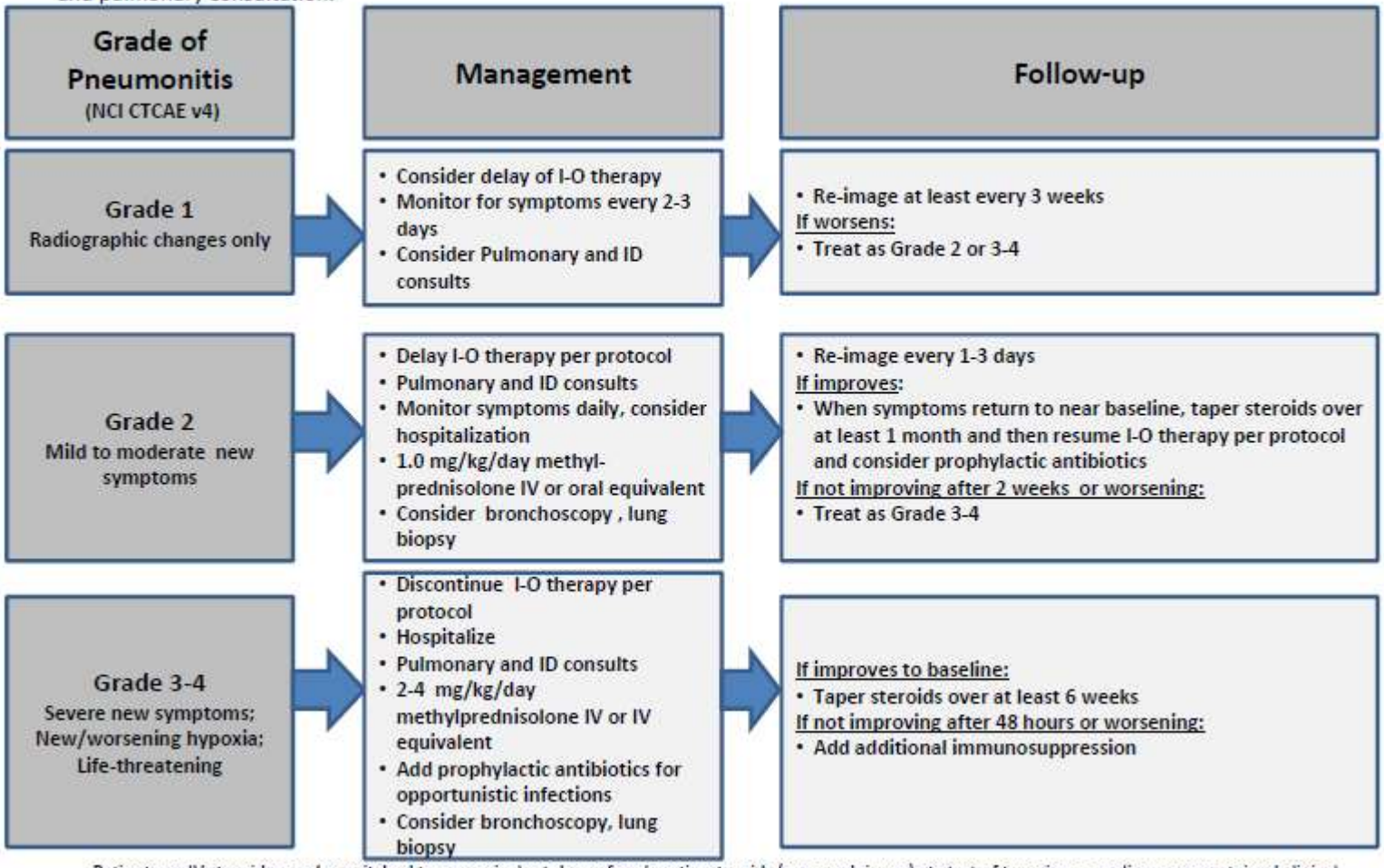


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

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.

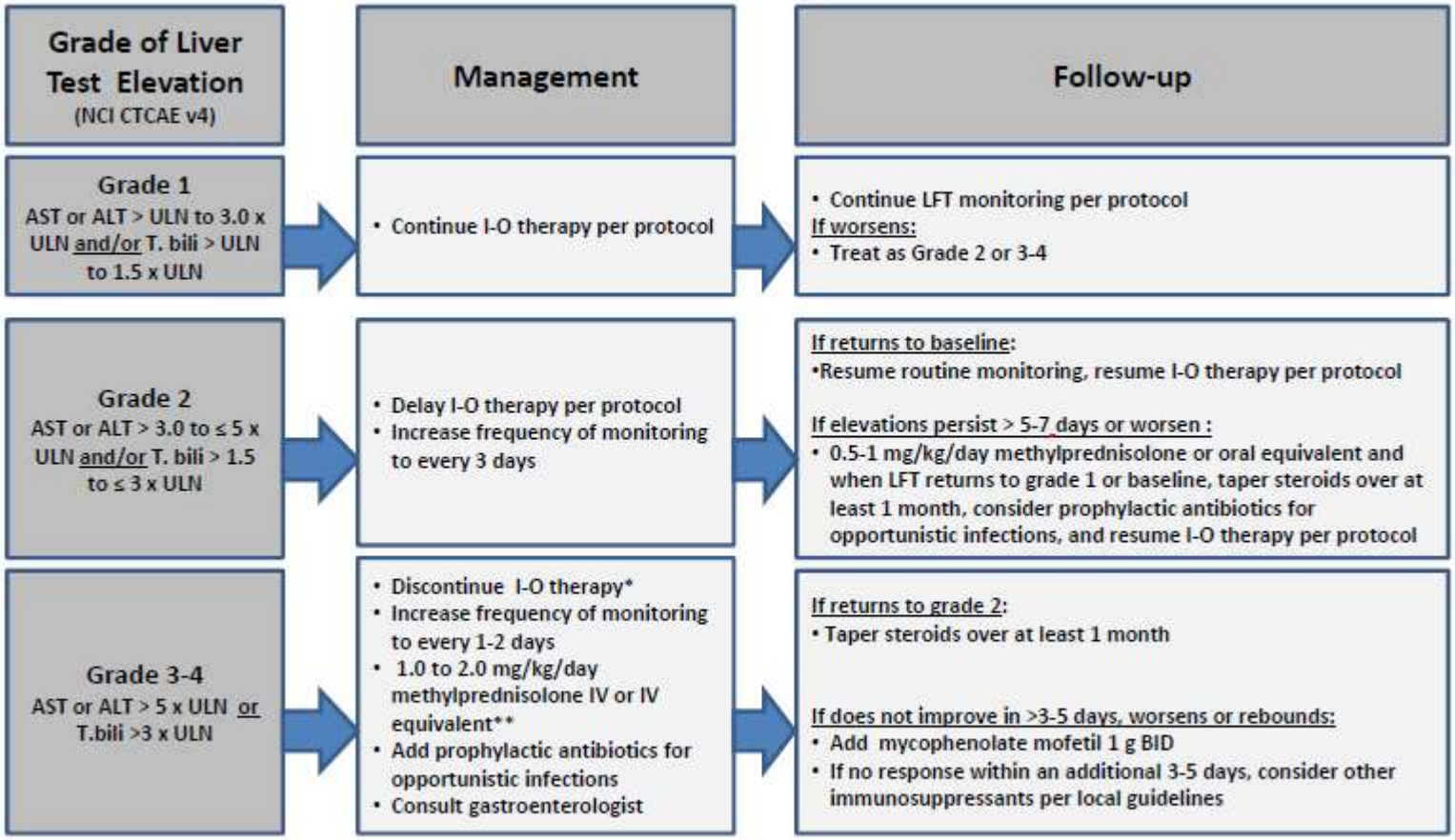


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

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.

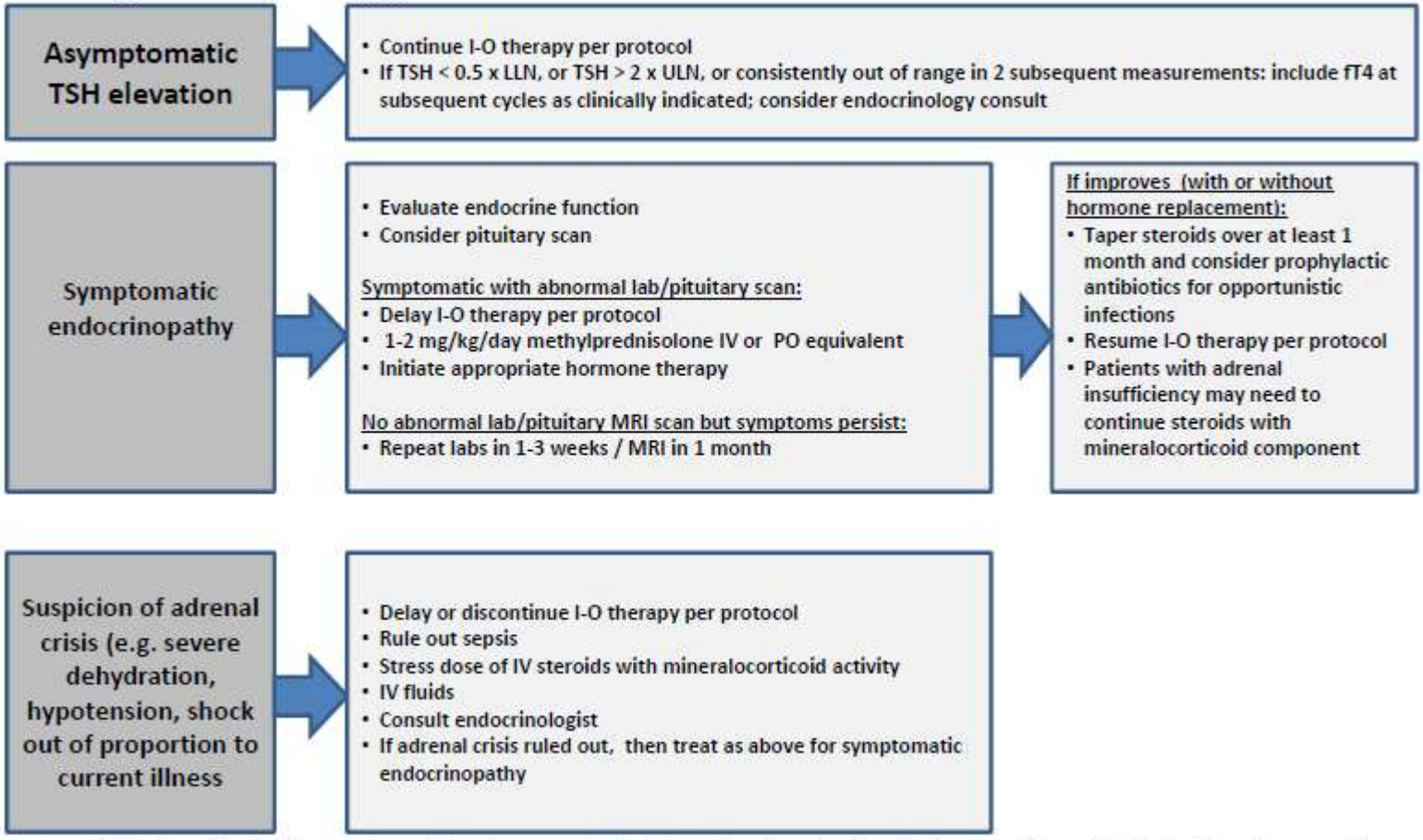
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

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

Updated 05-Jul-2016

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.

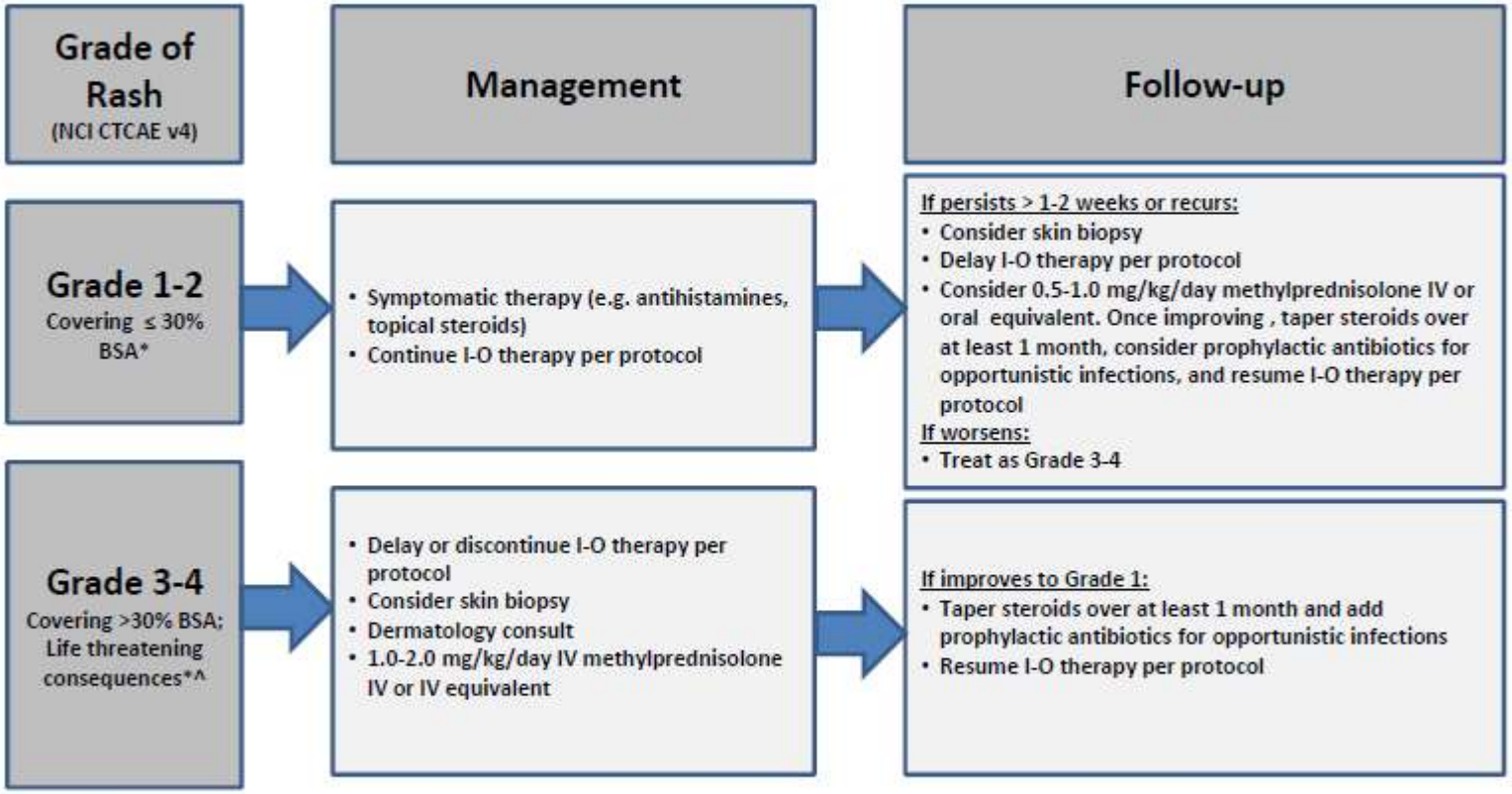


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Skin Adverse Event Management Algorithm

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

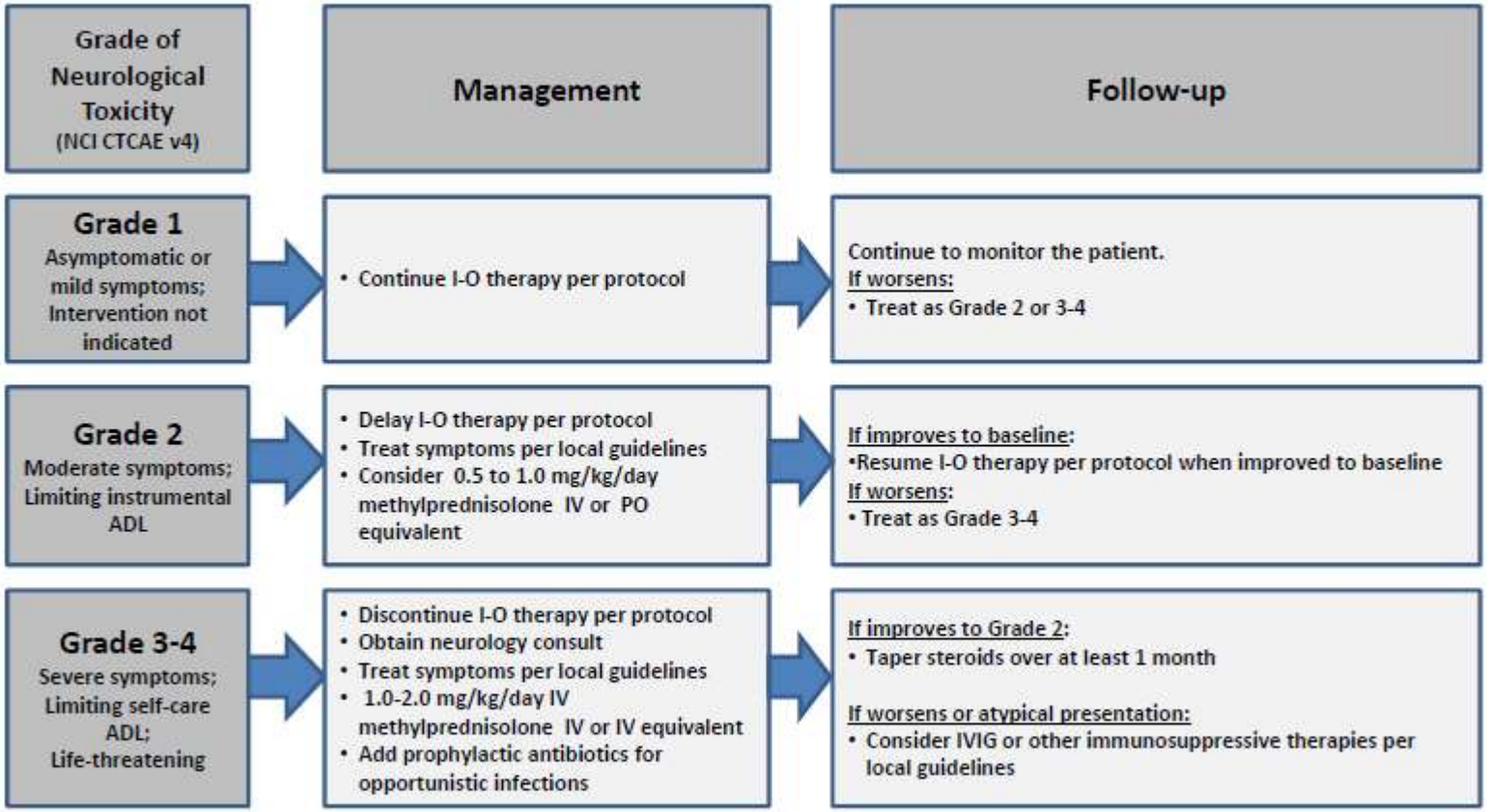


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Neurological Adverse Event Management Algorithm

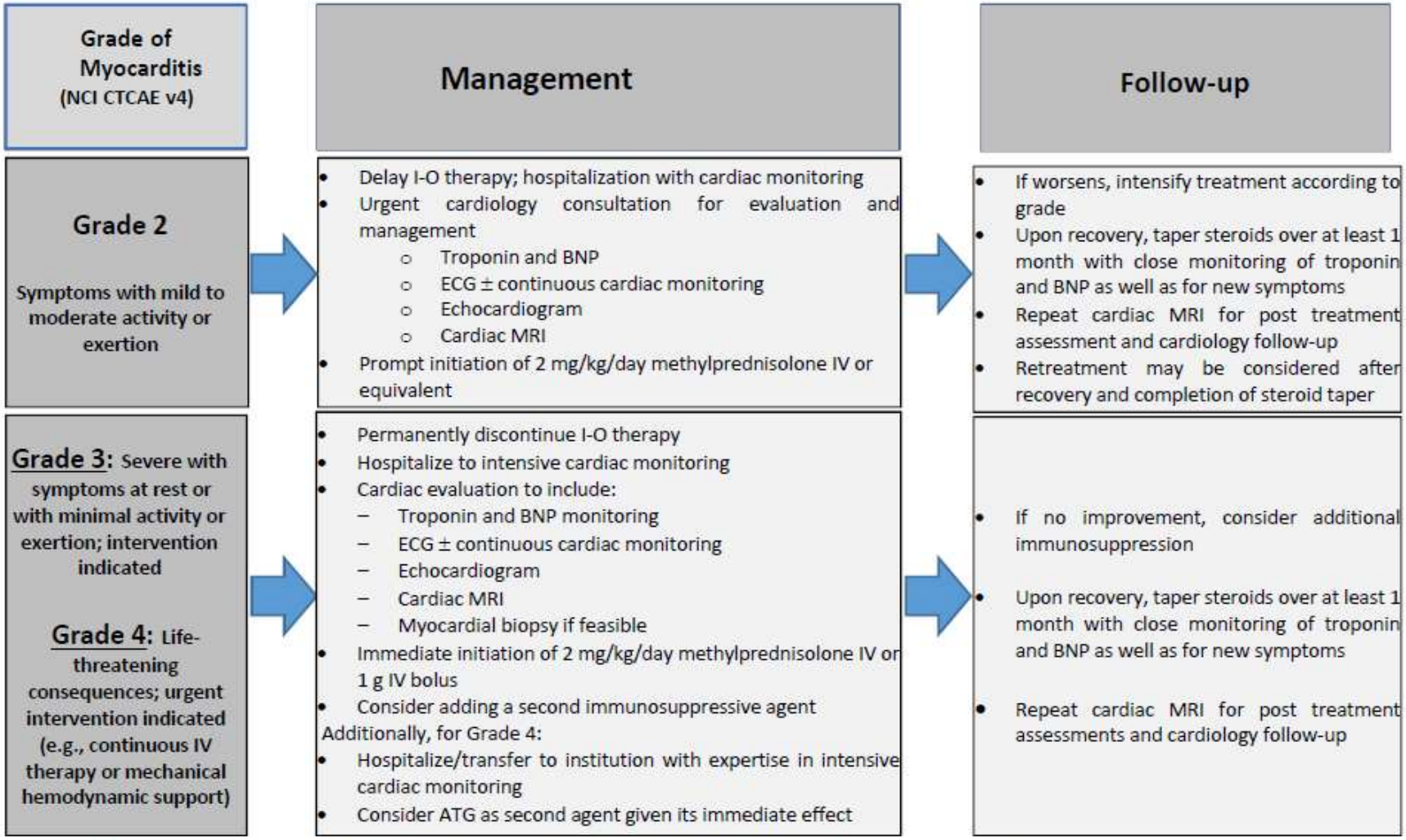
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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.

Updated 05-Jul-2016

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, 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.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.
ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging