Phase II Study of Nivolumab and Ramucirumab for Patients with Previously-Treated Mesothelioma: Hoosier Cancer Research Network LUN15-299

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PROTOCOL SIGNATURE PAGE

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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, or the applicable laws and regulations of the country of the study site for which I am responsible, 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).

Instructions to the investigator: Please **SIGN** and **DATE** this signature page. **PRINT** your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Scan and email the completed form to HCRN and keep a record for your files.

_____ _____

Signature of Site Investigator Date

_____
Site Investigator Name (printed)

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Site Investigator Title

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Name of Facility

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Location of Facility (City and State)

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STUDY SYNOPSIS

TITLE	Phase II Study of Nivolumab and Ramucirumab for Patients with Previously-Treated Mesothelioma
PHASE	Phase II
OBJECTIVES	**Primary Objectives** • Evaluate response rate [complete response (CR) + partial response (PR)] of nivolumab in combination with ramucirumab in subjects with previously-treated mesothelioma. Response assessment will be performed using modified RECIST 1.1 criteria as described by Byrne et al. [35]. **Secondary Objective(s)** • Characterize adverse effects (AE) of nivolumab in combination with ramucirumab in subjects with previously-treated mesothelioma. • Measure progression-free survival (PFS) rate at 24 weeks with the combination of the anti-Programmed Death 1 (PD-1) agent, nivolumab and the anti-vascular endothelial growth factor receptor 2 (VEGFR2) antibody, ramucirumab in subjects with previously-treated mesothelioma. • Measure overall survival (OS) at 2 years after treatment with nivolumab in combination with ramucirumab in subjects with previously-treated mesothelioma. **Correlative Objectives** • Correlate programmed death-ligand 1 (PD-L1) expression in tumor tissue (from biopsy before treatment) with best clinical response (modified RECIST 1.1 criteria) in subjects with previously-treated mesothelioma. • Correlate change in PD-L1 expression in tumor tissue from before therapy (assessed within 14 days before treatment) to after 4 cycles (8 weeks) of therapy with best clinical response (modified RECIST 1.1 criteria) at the end of Cycle 4 (Week 8) in subjects with previously-treated mesothelioma. • Correlate cytokine genes expressions and change in tumor tissue (such as IL-1, IL-2, IL-6, GM-CSF, IL-10, IL-12, T-bet, IRF1, IFNγ, CXCL1, CXCL9, CXCL10, CCL2 and 5) from before therapy (assessed within 14 days before treatment) to after 4 cycles (8 weeks) of therapy with best clinical response (modified RECIST 1.1 criteria) at the end of Cycle 4 (Week 8) in subjects with previously-treated mesothelioma. • Correlate change in soluble PD-L1 level in plasma during therapy (assessed pre-dose Cycles 1 and 5 [Days 1 and 57 of treatment period, respectively]), with best clinical response (modified RECIST 1.1 criteria) at the end of Cycle 4 (Week 8) in subjects with previously-treated mesothelioma.

	• Correlate change in number of CD8+, Granzyme B+ T cells in tumor tissue from before therapy (assessed within 14 days before treatment) to after 4 cycles (8 weeks) of therapy with best clinical response (modified RECIST 1.1 criteria) at the end of Cycle 4 (Week 8) in subjects with previously-treated mesothelioma.
STUDY DESIGN	Single arm, phase II cohort study
KEY ELIGIBILITY CRITERIA (See Section 3 for full eligibility criteria)	1. Male or female ≥ 18 years of age at time of consent. 2. Histologically-confirmed malignant mesothelioma not amenable to curative surgery and who have received at least one pemetrexed-containing chemotherapy regimen. 3. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 4. Adequate hepatic function within 28 days prior to study registration defined as meeting **all** of the following criteria: • total bilirubin < 1.5 mg/dL (25.65 μmol/L) **OR** direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 mg/dL (except subject with Gilbert's Syndrome, who can have total bilirubin < 3.0 mg/dl) • aspartate aminotransferase (AST) ≤ 3 × ULN or ≤ 5 × ULN for subjects with known hepatic metastases • alanine aminotransferase (ALT) ≤ 3 × ULN or ≤ 5 × ULN for subjects with known hepatic metastases 5. Adequate hematologic function within 28 days prior to study registration defined as meeting all of the following criteria: • hemoglobin ≥ 8 g/dL, subjects requiring transfusion will not be eligible to start study • and absolute neutrophil count (ANC) ≥ 1.5×10^9/L • and platelet count ≥ 100×10^9/L 6. Adequate renal function within 28 days prior to study treatment by **either** of the following criteria: • Serum creatinine ≤ 1.5 the ULN • if serum creatinine > 1.5 the ULN, estimated glomerular filtration rate (GFR) ≥ 40 mL/min 7. Adequate coagulation functioning within 28 days prior to study registration defined by either of the following criteria: • INR ≤1.5, and a partial thromboplastin time (PTT) (PTT/aPTT) < 1.5 x ULN (unless receiving anticoagulant therapy) • Subjects on full-dose anticoagulant must be on a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin (LMWH). Patients receiving warfarin must be switched to low molecular weight heparin and have achieved stable coagulation profile prior to first dose of protocol therapy. See section 3.1 for additional information.

	8. Subjects must be willing to undergo a CT-guided biopsy (i.e., image-guided percutaneous lung biopsy) to obtain tumor tissue within 28 days before initiation of treatment and after 4 cycles (8 weeks) of treatment. 9. Women of childbearing potential (WOCP) must not be pregnant (confirmed by a negative pregnancy test: a serum β-HCG with a sensitivity of 50 mIU/ml within 24 hours of study registration or urine dipstick) or breast-feeding. Women are not considered to be of childbearing potential provided they meet at least one of the following: 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year), or 3) not heterosexually active for the duration of the study. 10. Women of childbearing potential (WOCP) must be willing to birth control as outlined in Section 5.6.2. 11. Men who are not surgically or medically sterile must agree to use contraception as outlined in Section 5.6.2. 12. Measurable disease, defined as at least 1 tumor that fulfills the criteria for a target lesion according to modified RECIST 1.1 criteria and obtained by imaging within 28 days prior to prior to study registration. 13. Prior intracavity cytotoxic or sclerosing agents (including bleomycin) is acceptable. 14. Radiation therapy must be completed > 28 days of study registration, and the measurable disease must be outside of the radiation port. 15. Pemetrexed-containing chemotherapy must be completed > 28 days of study registration. 16. No prior malignancy is allowed except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, localized Gleason ≤ grade 7 prostate cancers. Subjects with other solid tumors treated curatively and without evidence of recurrence for at least 3 years prior to enrollment may be eligible for study after discussion with the sponsor-investigator
TREATMENT PLAN	Dosing will occur in 2-week cycles. On Day 1 of each cycle, the nivolumab intravenous infusion is given first followed 60 minutes later (first two cycles) or 15-30 minutes later (subsequent cycles) by the ramucirumab infusion. Nivolumab will be administered as a 30-minute intravenous infusion dosed at a flat dose of 240 mg. Ramucirumab will be administered as a 60-minute intravenous infusion dosed at 8 mg/kg. A scheduled blood draw for research purposes will occur prior to the nivolumab infusion on Day 1 of Cycles 1 and 5. Research biopsies will be done within 14 days of starting treatment and after 4 cycles (8 weeks) of treatment.
STATISTICAL CONSIDERATIONS	The primary study endpoint is the response rate [complete response (CR) + partial response (PR)] of patients for the therapy. A previous study identified a response rate of 20% for pembrolizumab, an anti PD-1 agent, in patients with malignant mesothelioma [39]. We hypothesize a response rate

	of 40%. Controlling for a probability of Type I error at 0.05 (one-sided), our sample size is estimated to be 33 to ensure 80% statistical power in successfully detecting an alternative response rate of 0.40, compared to a null rate of 0.20. With estimated up to 5% of patients that are not evaluable for primary endpoint, sample size will be increased to 35. Sample size analyses were conducted using the PASS software (NCSS, Kaysville, Utah, USA).
TOTAL NUMBER OF SUBJECTS	35 subjects
ESTIMATED ENROLLMENT PERIOD	Estimated 24 months
ESTIMATED STUDY DURATION	Estimated 36 months

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SCHEMA

Phase II Study of Nivolumab and Ramucirumab for Patients with Previously-Treated Mesothelioma.
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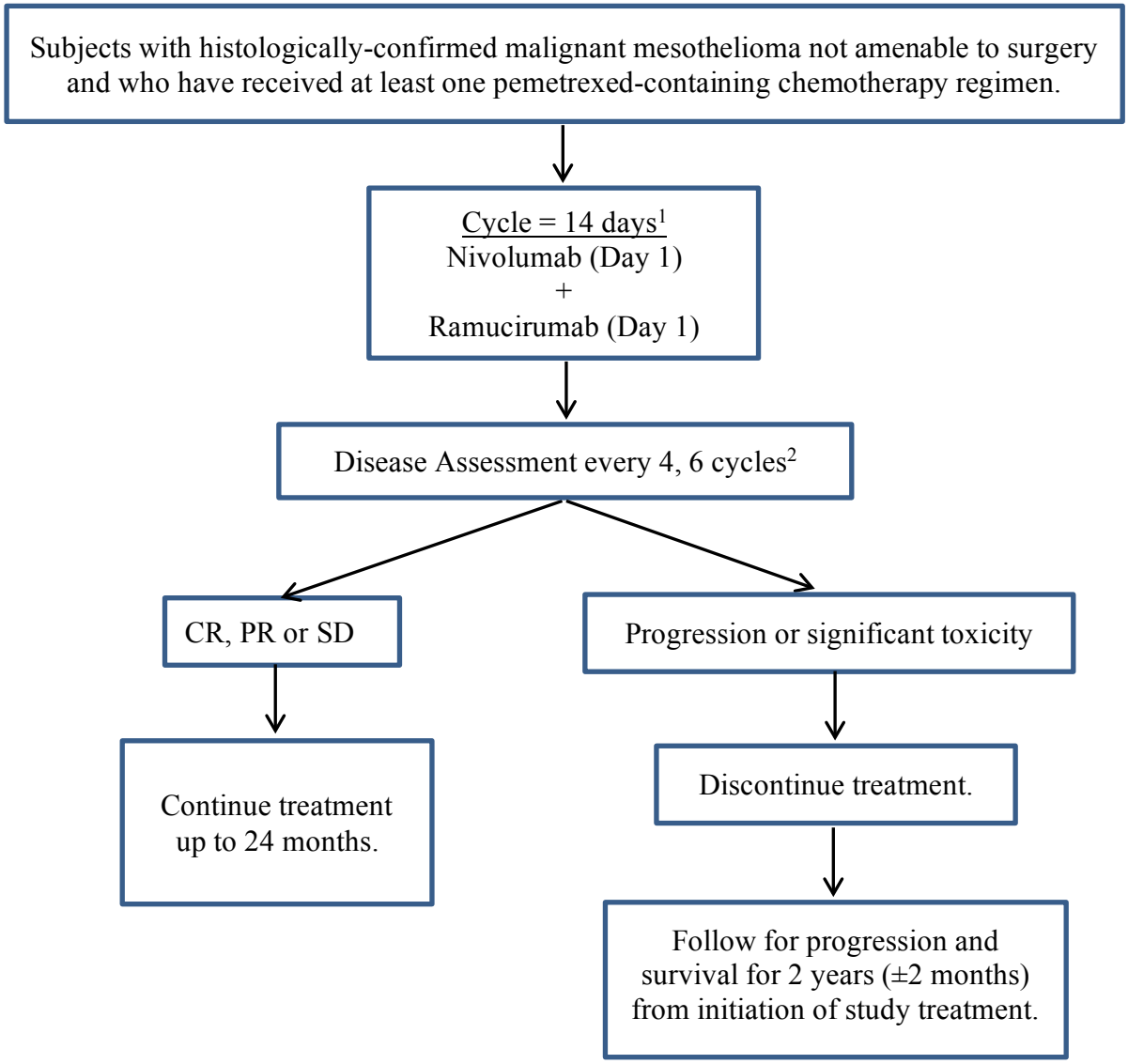

[1]: Treatment with 240 mg nivolumab infused over 30 min followed by 8 mg/kg ramucirumab infused over 60 min.

- For the first two cycles, the infusions will be separated by a 60-minute interval.
- For cycle 3 and beyond, the infusions will be separated by a 15-30 minute interval, provided the subject did not show any untoward effects during the first two cycles.

[2]: Disease assessment will be performed every 4 cycles (8 weeks) for 6 months, then every 6 cycles (12 weeks) until disease progression for a maximum of 2 years from initiation of study treatment.

ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ANC	absolute neutrophil count
Anti-PD-1 antibody	anti-programmed death 1 antibody
Anti-PD-L1 antibody	anti-programmed death-ligand 1 antibody
ALK	Anaplastic lymphoma kinase
ALT	alanine aminotransferase
aPTT	Activated partial thromboplastin time
ASCO	American society of clinical oncology
AST	aspartate aminotransferase
ATE	arterial thromboembolic event
BCG	Bacillus Calmette–Guérin
CCL	chemokine (C-C motif) ligand
CI	Confidence interval
CIK	cytokine-induced killer
cm	centimeter
CNS	Central nervous system
CR	complete response
CT	computed tomography
CTC	cytotoxic T cell
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTLA4	cytotoxic T-lymphocyte-associated antigen 4
CXCL	chemokine (C-X-C motif) ligand
DCR	disease control rate
DILI	drug-induced liver injury
DKA	diabetic ketoacidosis
dL	deciliter
DSMC	Data Safety Monitoring Committee
eCRF	electronic case report form
EDC	electronic data capture
ECOG	Eastern Cooperative Oncology Group
eGFR	Estimated Glomerular Filtration Rate

GFR	Glomerular filtration rate
GM-CSF	granulocyte-macrophage colony-stimulating factor
HR	Hazard ratio
HCl	Hydrochloric acid
HCRN	Hoosier Cancer Research Network
Hgb	hemoglobin
HIF-1	hypoxia-inducible factor-1
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
hr	hour
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFNγ	interferon gamma
IHC	immunohistochemistry
IgG	Immunoglobulin G
IL	interleukin
IND	Investigational New Drug
INR	international normalized ratio
I/O	input/output
IRB	Institutional Review Board
irDCR	Immune-related disease control rate
IRF1	Interferon regulatory factor 1
IV	intravenous
kg	kilogram
lb	pound
LD	long diameter
MDSC	myeloid-derived suppressor cell
mg	milligram
min	minute
mL	milliliter
mm^3	cubic millimeters
MRI	Magnetic resonance imaging
N/A	Not applicable
NaOH	Sodium hydroxide
NCI	National Cancer Institute

NDC	National Drug Code
NK Cells	Natural Killer Cells
NS	Normal saline
NSAID	Non-steroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
OS	overall survival
PD	Progressive disease
PD-1	programmed death 1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PET-CT	positron emission tomography/ computed tomography
PFS	progression-free survival
PT	Prothrombin time
PTT	Partial thromboplastin time
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
RPLS	Reversible Posterior Leukoencephalopathy Syndrome
RR	response rate
SAE	serious adverse event
SD	stable disease
T1DM	Type 1 diabetes mellitus
T3	Triiodothyronine
T4	Free thyroxine
TAM	tumor-associated macrophage
TSH	Thyroid stimulating hormone
UA	urinalysis
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
VEGF	Vascular endothelial growth factor
VEGFR2	Vascular endothelial growth factor receptor 2
VTE	Venous thromboembolism
WOCP	women of childbearing potential
wt	weight

1. BACKGROUND AND RATIONALE

1.1. Introduction

Malignant mesothelioma is a rare yet highly aggressive cancer for which radiation and surgical therapy are typically poor options. Cisplatin in combination with pemetrexed is now a standard first-line treatment for malignant mesothelioma [1]. However, once patients fail treatment with a pemetrexed-containing regimen, there is no standard of care available.

Anti-angiogenic therapy in conjunction with standard platinum and anti-folate chemotherapy has been shown to be effective in malignant mesothelioma patients. In a recently presented multicenter study with 445 patients, Zalcman et al. showed that the addition of bevacizumab, an anti- vascular endothelial growth factor (VEGF) monoclonal antibody, to standard cisplatin and pemetrexed resulted in improved progression-free and overall survival [2]. Progression-free survival (PFS) was median 9.6 months (95% confidence interval [CI]: 8.5-10.6) in bevacizumab arm vs. 7.5 months (95% CI: 6.8-8.1) in the reference arm (adj. hazard ratio (HR) = 0.62, 95% CI [0.50-0.75], $p < 0.0001$). Overall survival was median: 18.8 months (95% CI: 15.9-22.6) vs. 16.1 months (95% CI: 14.0-17.9) for the reference arm, (adj. HR = 0.76 [95% CI: 0.61; 0.94], $p = 0.012$). Additionally, added toxicity was minimal with similar rates of G3-4 hematologic events in both arms. Hypertension, proteinuria, hemorrhage and thrombotic events were in line with previously reported rates for bevacizumab in other cancer types.

Immunotherapy of cancer became a very attractive concept after the recent introduction of checkpoint inhibitors. In a recently presented study describing the effect of a CTLA4 targeting antibody, in second line therapy of mesothelioma, 29 patients were treated with tremelimumab. The study met its primary endpoint since at a median follow-up of 14.5 months, 4 immune-related partial responses (irPR) were observed. Eleven patients had stable disease of median duration 7.7 months (range 2.6-16.6+), and the related immune-related disease control rate (irDCR) was 51.7%. Median overall survival (OS) was 11.3 months (95% CI: 5.6-17.0) [3]. The results of this study led to an ongoing "Randomized, double-blind, placebo-controlled study of tremelimumab for second- and third-line treatment of unresectable pleural or peritoneal mesothelioma" study" (NCT01843374).

Thus, there are two potential treatment options for patients with mesothelioma who have failed on first-line treatment with a pemetrexed-containing regimen: immunotherapy and anti-angiogenic (anti-VEGF) therapy. After describing one mode of immunotherapy in more detail below, including its effects on another lung cancer, non-small cell lung cancer (NSCLC), we present the case that combining immunotherapy with anti-angiogenic therapy might provide a more efficacious response to using immunotherapy alone.

The Programmed Death 1 (PD-1) Receptor, Its Programmed death-ligand 1 (PD-L1), and a Novel Immunotherapy: Anti-PD-1 Antibody

An increasing body of evidence, both from lab based animal models and from clinical epidemiology, suggests that the immune system operates as a significant barrier to tumor formation and progression. One of the hallmarks of cancer is its ability to evade immune destruction. The Programmed death 1 (PD-1) receptor is expressed on activated T- and B-cells. Its major ligand Programmed death-ligand 1 (PD-L1) is typically expressed on a subset of

macrophages, but can be induced by inflammatory cytokines in a variety of tissue types [4-8]. When activated T-cells expressing PD-1 encounter PD-L1, T-cell effector functions are diminished. PD-1 also binds PD-L2 (B7-DC), which is expressed selectively on macrophages and dendritic cells [8-10]. These unique expression patterns suggest that PD-L1 promotes self-tolerance in peripheral tissues, while PD-L2 may function in lymphoid organs, although the role of PD-L2 in immunomodulation is not as well understood [11]. Multiple tumor types have been shown to express PD-L1 and PD-L2, effectively co-opting a native tolerance mechanism [12-15]. Especially pertinent to this protocol is the fact that PD-L1 is highly expressed on mesothelioma tumor cells and within the tumor stroma [16]. It has been postulated that antibodies that block the interaction between PD-1 and PD-L1 in tumors may preferentially release the cytotoxic function of tumor-specific T cells with fewer systematic toxic effects than those that are seen with other immune checkpoint inhibitors, such as CTLA-4 [17].

Two large, dose-escalation, phase 1 clinical trials evaluating the safety of the anti–PD-1 antibody nivolumab (formerly known as BMS936558) and the anti–PD-L1 antibody BMS936559 showed significant antitumor activity in subjects with advanced melanoma, lung carcinoma, and renal cell carcinoma, among other cancers, thus validating the PD-1–PD-L1 axis as a therapeutic target [18-20]. Most clinical responses were durable beyond 1 year [19,20]. Toxic effects were generally of low grade.

A recent randomized, open-label, phase 3, international study comparing nivolumab to docetaxel in patients with advanced squamous-cell non–small cell lung cancer who had disease progression during or after first-line chemotherapy showed that OS, PFS and response rate (RR) were significantly better with nivolumab than docetaxel. The median overall survival was 9.2 months (95% confidence interval [CI], 7.3 to 13.3) with nivolumab versus 6.0 months (95% CI, 5.1 to 7.3) with docetaxel. The risk of death was 41% lower with nivolumab than with docetaxel (HR, 0.59; 95% CI, 0.44 to 0.79; $p<0.001$). At 1 year, the OS rate was 42% (95% CI, 34 to 50) with nivolumab versus 24% (95% CI, 17 to 31) with docetaxel. The RR was 20% with nivolumab versus 9% with docetaxel ($P=0.008$). The median PFS was 3.5 months with nivolumab versus 2.8 months with docetaxel (HR for death or disease progression, 0.62; 95% CI, 0.47 to 0.81; $p<0.001$). Treatment-related adverse events of grade 3 or 4 were reported in 7% of the patients in the nivolumab group as compared with 55% of those in the docetaxel group [21].

Despite the renewed hope for cancer immunotherapy, survival benefits from adoptive cell immunotherapy alone remain modest. One of the critical challenges that adoptive cell immunotherapy faces is the immunosuppressive tumor microenvironment. The tumor microenvironment contains a vasculature that is structurally and functionally abnormal. In certain regions of tumors, the vessels are leaky, twisted, and lack stabilizing pericytes and basement membrane. The structurally abnormal tumor vessels do not provide nutritive blood flow. The immature tumor vessels contribute to an abnormal tumor microenvironment with one of the key characteristics being that of hypoxia [22]. Abnormal tumor vasculature and subsequent tumor hypoxia contribute to immune tolerance of tumor cells by impeding the homing of cytotoxic T cells into tumor parenchyma and inhibiting their antitumor efficacy [23]. These obstacles might explain why the promising approach of adoptive cell immunotherapy does not exert significant antitumor activity [24]. Hypoxia contributes to immune suppression by activating hypoxia-inducible factor (HIF-1) and the VEGF pathway, which plays a determining

role in promoting tumor cell growth and survival [25]. Tumor hypoxia creates an immunosuppressive microenvironment via the accumulation and subsequent polarization of inflammatory cells toward immune suppression phenotypes, such as myeloid-derived suppressor cells (MDSC) [26], tumor-associated macrophages (TAM) [27], and dendritic cells [28]. Adoptive cell immunotherapy alone is not efficient enough to decrease tumor growth as its antitumor effect is inhibited by the immunosuppressive hypoxic tumor microenvironment.

Antiangiogenic therapy could normalize tumor vasculature and decrease hypoxic tumor area and thus may be an effective modality to potentiate immunotherapy.
Recent studies have demonstrated that there is an interaction between immune response and tumor angiogenesis. Huang et al. demonstrated that lower doses of an anti-VEGF receptor 2 (VEGFR2) antibody treatment enhanced the anti-cancer efficacy of a vaccine therapy in a model of immune tolerant breast cancer [29]. Furthermore, it was demonstrated that lower doses of the same anti-angiogenic treatment normalized breast tumor vasculature and improved tissue distribution of functional vasculature within the tumor. As stated earlier, myeloid-derived suppressor cells (MDSC) and tumor-associated macrophages (TAM) promote tumor progression by suppressing innate anti-cancer immunity. Low doses of this treatment decreased the number of MDSCs and increased the number of TAMs. On profile analysis, however, these TAMs were polarized from an immunosuppressive (M2-like) to an immune-stimulatory (M1-like) phenotype. A low dose of the anti-angiogenic treatment was also demonstrated to enhance tumor infiltration by CD4+ and CD8+ T-cells. An improvement in tumor vasculature and polarization of TAMs was shown to reduce immune-regulatory signals, and facilitated recruitment of activated CD8+ T cells that could exact an anti-tumor effect.

Similarly, Shi et al. demonstrated that using an anti-angiogenic agent rh-endostatin improved the anti-cancer effect of adoptive cytokine-induced killer (CIK) cells against lung carcinoma [30]. The proposed mechanism was a synergistic therapeutic effect in which endostatin contributed to structural normalization of tumor vasculature. They also demonstrated that the addition of endostatin augmented homing of the CIK cells and intratumoral CD3(+) T lymphocytes, suggesting that the addition of an anti-angiogenic agent normalized vasculature, reduced hypoxia and altered the tumor microenvironment to enhance tumor infiltration by transferred CIK cells and T-lymphocytes.

Ramucirumab (IMC-1121B) is a fully human monoclonal antibody (IgG1) developed for the treatment of solid tumors. It is directed against the VEGFR2. By binding to VEGFR2 it works as a receptor antagonist blocking the binding of VEGF to VEGFR2. VEGFR2 is known to mediate the majority of the downstream effects of VEGF in angiogenesis. On April 21, 2014, the FDA approved ramucirumab as a single agent or with paclitaxel, for treatment of advanced gastric or gastro-esophageal junction adenocarcinoma if the disease has progressed despite fluoropyrimidine- or platinum-containing chemotherapy [31,32]. On December 12, 2014, the FDA approved ramucirumab in combination with docetaxel, for treatment of metastatic NSCLC with disease progression on or after platinum-containing chemotherapy [33].

1.2. Study Rationale

The programmed death ligand 1 (PD-L1) [16] and VEGFR2 [34] are highly-expressed on mesothelioma cells, and are therefore attractive options for this cancer. We chose to study the combination of ramucirumab with nivolumab because of the potential efficacy of these two agents in mesothelioma and because of the potential synergistic activity between them [30]. As previously discussed, immunotherapies such as anti-PD-1 inhibitors must contend with a hostile, immunosuppressive tumor microenvironment due to angiogenesis that results in hypoxia. This hypoxia decreases the ability of antibodies to infiltrate the tumor. We hypothesize that the normalization of tumor vasculature (by reducing the area of the tumor that is hypoxic) with an anti-VEGF strategy (i.e., ramucirumab) used in synergy with a PD-1 inhibitor will facilitate the infiltration of T-lymphocytes into tumor parenchyma. We will conduct a phase II study based on this premise using nivolumab and ramucirumab as second-line therapy in patients with malignant mesothelioma who have failed standard doublet platinum and anti-folate therapy.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

- Evaluate response rate [complete response (CR) + partial response (PR)] of nivolumab in combination with ramucirumab in subjects with previously-treated mesothelioma. Response assessment will be performed using modified RECIST 1.1 criteria as described by Byrne et al. [35].

2.1.2. Secondary Objectives

- Characterize adverse effects (AE) of nivolumab in combination with ramucirumab in subjects with previously-treated mesothelioma.
- Measure progression free survival (PFS) rate at 24 weeks with the combination of the anti PD-1 agent, nivolumab and the anti VEGFR2 antibody, ramucirumab in subjects with previously-treated mesothelioma.
- Measure overall survival (OS) at 2 years after treatment with nivolumab in combination with ramucirumab in subjects with previously-treated mesothelioma.

2.1.3. Correlative Objectives

- Correlate PD-L1 expression in tumor tissue (from biopsy before treatment) with best clinical response (modified RECIST 1.1 criteria) in subjects with previously-treated mesothelioma.
- Correlate change in PD-L1 expression in tumor tissue from before therapy (assessed within 14 days before treatment) to after 4 cycles (8 weeks) of therapy with best clinical response (modified RECIST 1.1 criteria) at the end of Cycle 4 (Week 8) in subjects with previously-treated mesothelioma.
- Correlate cytokine genes expressions in tumor tissue (such as IL-1, IL-2, IL-6, GM-CSF, IL-10, IL-12, T-bet, IRF1, IFNγ, CXCL1, CXCL9, CXCL10, CCL2 and 5) from before therapy (assessed within 14 days before treatment) to after 4 cycles (8 weeks) of therapy with best clinical response (modified RECIST 1.1 criteria) at the end of Cycle 4 (Week 8) in subjects with previously-treated mesothelioma.

- Correlate change in soluble PD-L1 level in plasma during therapy (assessed pre-dose Cycles 1 and 5 [(Days 1 and 57 of treatment period, respectively]) relative to baseline with best clinical response (modified RECIST 1.1 criteria) at the end of Cycle 4 (Week 8) in subjects with previously-treated mesothelioma.
- Correlate change in number of CD8+, Granzyme B+ T cells in tumor tissue from before and during therapy (assessed within 14 days before treatment) to after 4 cycles (8 weeks) of therapy with best clinical response (modified RECIST 1.1 criteria) at the end of Cycle 4 (Week 8) in subjects with previously-treated mesothelioma.

3. ELIGIBILITY CRITERIA

Study entry is open to adults regardless of gender or ethnic background. While there will be every effort to seek out and include women and minorities, the subject population is expected to be no different than that of other advanced solid tumor cancer studies at each participating institution.

3.1. Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Male or female ≥ 18 years of age at time of consent.
2. Histologically-confirmed malignant mesothelioma not amenable to curative surgery and who have received at least one pemetrexed-containing chemotherapy regimen.
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
4. Adequate hepatic function within 28 days prior to study registration defined as meeting all of the following criteria:
    - total bilirubin < 1.5 mg/dL (25.65 μmol/L) OR direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 mg/dL (except subject with Gilbert's Syndrome, who can have total bilirubin < 3.0 mg/dl)
    - aspartate aminotransferase (AST) ≤ 3 × ULN or ≤ 5 × ULN for subjects with known hepatic metastases
    - alanine aminotransferase (ALT) ≤ 3 × ULN or ≤ 5 × ULN for subjects with known hepatic metastases
5. Adequate hematologic function within 28 days prior to study registration defined as meeting all of the following criteria:
    - hemoglobin ≥ 8 g/dL, subjects requiring transfusion will not be eligible to start study
    - and absolute neutrophil count (ANC) ≥ 1.5×10^9/L
    - and platelet count ≥ 100×10^9/L
6. Adequate renal function within 28 days prior to study registration by either of the following criteria:
    - serum creatinine ≤1.5 times the ULN, or creatinine clearance (measured via 24-hour urine collection) ≥40 mL/minute (that is, if serum creatinine is >1.5 times the ULN, a 24-hour urine collection to calculate creatinine clearance must be performed)
    - subject's urinary protein is ≤1+ on dipstick or routine urinalysis (UA; if urine dipstick or routine analysis is ≥2+, a 24-hour urine collection for protein must demonstrate <1000 mg of protein in 24 hours to allow participation in this protocol)

7. Adequate coagulation functioning within 28 days prior to study registration defined by either of the following criteria:
    - INR $\leq$ 1.5, and a partial thromboplastin time (PTT) (PTT/aPTT) < 1.5 x ULN (unless receiving anticoagulant therapy)
    - Subjects on full-dose anticoagulation must be on a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin (LMWH). Patients receiving warfarin must be switched to low molecular weight heparin and have achieved stable coagulation profile prior to first dose of protocol therapy. For heparin and LMWH there should be no active bleeding (that is, no bleeding within 14 days prior to first dose of protocol therapy) or pathological condition present that carries a high risk of bleeding (for example, tumor involving major vessels or known varices).
8. Subjects must be willing to undergo a CT-guided biopsy (i.e., image-guided percutaneous lung biopsy) to obtain tumor tissue within 28 days before initiation of treatment and after 4 cycles (8 weeks) of treatment.
9. Women of childbearing potential (WOCP) must be willing to use birth control as outlined in Section 5.6.2.
10. Men who are not surgically or medically sterile must agree to use contraception as outlined in Section 5.6.2.
11. Measurable disease, defined as at least 1 tumor that fulfills the criteria for a target lesion according to modified RECIST 1.1 criteria, and obtained by imaging within 28 days prior to study registration.
12. Prior intracavity cytotoxic or sclerosing agents (including bleomycin) is acceptable.
13. Radiation therapy must be completed > 28 days before study registration, and the measurable disease must be outside of the radiation port.
14. Pemetrexed-containing chemotherapy must be completed > 28 days before study registration.
15. Must provide written informed consent and HIPAA authorization approved by an Institutional Review Board (IRB). NOTE: HIPAA authorization may be included in the informed consent or obtained separately.
16. All previous toxicity resolved to Grade 1 or less.

3.2. Exclusion Criteria

1. Any Grade 3-4 GI bleeding within 3 months prior to study registration.
2. History of deep vein thrombosis, pulmonary embolism, or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered "significant") during the 3 months prior to study registration.
3. Any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within 6 months prior to study registration.
4. Cirrhosis at a level of Child-Pugh B (or worse), or cirrhosis (any degree) with a history of hepatic encephalopathy, or clinically meaningful ascites resulting from cirrhosis. Clinically meaningful ascites is defined as ascites from cirrhosis requiring diuretics or paracentesis.
5. Uncontrolled or poorly-controlled hypertension (>160 mmHg systolic or > 100 mmHg diastolic for >4 weeks) despite standard medical management.

6. Prior history of GI perforation/fistula (within 6 months of study registration) or risk factors for perforation.
7. Serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to study registration.
8. Active brain metastases or carcinomatous meningitis. Subjects with neurological symptoms must undergo a head CT scan or brain MRI to exclude brain metastasis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of study drugs and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 14 days prior to study registration. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.
9. Major surgery within 28 days prior to study registration
10. Subcutaneous venous access device placement within 7 days prior to study registration.
11. Elective or planned major surgery to be performed during the course of the clinical trial.
12. Is receiving chronic antiplatelet therapy, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents. Once-daily aspirin use (maximum dose 325 mg/day) is permitted.
13. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: HIV testing is not required.
14. Known history of testing positive for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody), indicating acute or chronic infection. NOTE: Hepatitis B and Hepatitis C testing is not required.
15. Condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
16. 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). Subjects are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.
    NOTE: Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
17. Received a live vaccine within 30 days prior to the first dose of trial treatment. Examples of live vaccines include, but are not limited to: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines and are not allowed.
18. History of interstitial lung disease or active, non-infectious pneumonitis.
19. Female subject is pregnant or breast-feeding.

NOTE: Women of childbearing potential (WOCP) must have a negative pregnancy test (either serum β-HCG with a sensitivity of 50 mIU/ml or urine dipstick within 24 hours of study registration).
NOTE: Women are not considered to be of childbearing potential if they meet at least one of the following: 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year), or 3) not heterosexually active for the duration of the study. See section 5.6.2.

20. Major blood vessel invasion or significant intratumor cavitation.
21. If they experience hemoptysis (defined as bright red blood or ≥ ½ teaspoon) within 2 months prior to first dose of protocol therapy or with radiographic evidence of intratumor cavitation or has radiologically documented evidence of major blood vessel invasion or encasement by cancer.
22. Any condition that, in the opinion of the investigator, might jeopardize the safety of the subject or interfere with protocol compliance.
23. Any mental or medical condition that prevents the subject from giving informed consent or participating in the trial.
24. Any pathological condition that carries a high risk of bleeding (for example, tumor involving major vessels or known varices.)
25. Known hypersensitivity to nivolumab or ramucirumab or any of their components.
26. Known history of active tuberculosis.
27. Received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
28. No prior malignancy is allowed except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, localized Gleason ≤ grade 7 prostate cancers. Subjects with other solid tumors treated curatively and without evidence of recurrence for at least 3 years prior to enrollment may be eligible for study after discussion with the sponsor-investigator
29. Treatment with any investigational agent within 28 days prior to study registration. The subject must have recovered from the acute toxic effects of the regimen.

4. SUBJECT REGISTRATION

All subjects must be registered through the Hoosier Cancer Research Network (HCRN) 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 after signing consent but prior to starting protocol therapy.

5. TREATMENT PLAN

5.1. Overall Design and Study Plan

The primary objective of this open label, non-randomized Phase II trial is to determine the activity of nivolumab in combination with ramucirumab in subjects with histologically-confirmed malignant mesothelioma not amenable to curative surgery and who have received at least one pemetrexed-containing chemotherapy regimen. The primary endpoint in this study is response rate (RR). Nivolumab and ramucirumab will be given on Day 1 of each 14-day cycle. Treatment will continue for up to 24 months (52 cycles) or until disease progression by RECIST 1.1 criteria, unacceptable toxicity, subject refusal, or subject death. Subjects who voluntarily stop the study, have progressive disease, or unacceptable toxicities will be followed for a total of 24 months after initiation of study treatment.

Correlative research analyses include examining the relationship between best clinical response overall with tissue PD-L1, and at the end of Cycle 4 (Week 8) with changes in soluble PD-L1, cytokine genes expressions and number of CD8+ and Granzyme B+ T cells in tumor tissue from before therapy to the end of Cycle 4 (Week 8). Research analyses also include examining the relationship between changes in soluble PD-L1 level, during therapy (assessed pre-dose Cycles 1 and 5 [Days 1 and 57 of treatment period, respectively]) with best clinical response (modified RECIST 1.1 criteria) at the end of Cycle 4 (Week 8).

5.2. Pre-medication

No premedication is indicated for nivolumab. However, for subjects who experience a Grade 1 or Grade 2 infusion reaction, prior to subsequent infusions it is recommended that diphenhydramine 50 mg (or equivalent) and/or paracetamol (acetaminophen) 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

Prior to ramucirumab infusion, IV diphenhydramine (or equivalent) will be given. For subjects who experience a Grade 1 or Grade 2 infusion-related reaction (IRR), premedication must be given for all subsequent infusions. If a subject has a second Grade 1 or Grade 2 IRR, administer dexamethasone 10 mg (or equivalent); for subsequent infusions, premedicate with the following (or equivalent): diphenhydramine hydrochloride (IV), acetaminophen, and dexamethasone.

5.3. Drug Administration

Drug	Dose	Length and route of administration	Frequency of administration	Length of cycle
Nivolumab (1st)	240 mg	30 min (-5/+10), IV	Day 1	14 days
Ramucirumab (2nd)	8 mg/kg	60 min (-5, +10), IV	Day 1	

NOTE: Infusions may be given ±3 days for reasons such as observed holidays, inclement weather, scheduling conflicts, etc. It should be clearly documented in subject's chart and case report forms. **NOTE:** there must be at least 12 days between each dose of nivolumab.

5.3.1. Sequencing of Nivolumab + Ramucirumab Administration

Dosing will occur in 2-week cycles. On Day 1 of each cycle, the nivolumab intravenous infusion is given first followed 60 minutes after the end of the infusion (first two cycles) or 15-30* minutes after the end of the infusion (subsequent cycles) by the ramucirumab infusion.

*The interval between infusions for subsequent cycles beyond Cycle 2 will be shortened to 15-30 minutes provided that subjects in the first two cycles show no untoward effects from nivolumab which would require a 60-minute observation period.

5.3.2. Nivolumab Dose and Administration

Nivolumab will be administered as a 30-minute intravenous infusion dosed at 240 mg. 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. 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 1 mg/mL. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

5.3.3. Ramucirumab Dose and Administration

Ramucirumab will be administered as a 60-minute intravenous infusion dosed at 8 mg/kg.

The dosing calculations should be based on the actual body weight at baseline. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the original dose, the dose must be recalculated. All doses should be rounded to the nearest milligram. There will be no dose modifications allowed.

5.3.4. Monitoring

- Vital signs including blood pressure, pulse, temperature, respirations, and pulse oximetry, will be measured as follows:
  - for the first two cycles of the nivolumab infusion: before, 5 min after start of the infusion, and 30 min (±5 min) after the end of the infusion;
  - if vital signs are stable for first two cycles, subsequent cycles: before and 5 min (±5 min) after the end of the infusion
  - Ramucirumab infusion: before the infusion, 30 min (±5 min) after the start of the infusion, and after (±5 min) the end of the infusion
- Subjects will be closely monitored for toxicities. Toxicity will be assessed using CTCAE version 4.

5.3.5 Dose Delay Due to Toxicity

If both drugs are held on Day 1 due to toxicity, the day treatment is resumed will be considered Day 1 of the cycle. If only one drug is held on Day 1 due to toxicity, the dose of that drug will <u>not</u> be made up.

5.4. Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events that are related to ramucirumab and nivolumab are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to ramucirumab or nivolumab.

5.4.1. Suggested supportive care measures for the management of adverse events that are related to ramucirumab

Infusion-Related Reactions

- Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.
- For guidelines on treatment holds, timing for restarting treatment or discontinuing treatment permanently, see Section 6.2.1, Table 2.

Proteinuria

- Treat proteinuria according to established guidelines.
- For guidelines on treatment holds, timing for restarting treatment or discontinuing treatment permanently, see Section 6.2.1, Table 2.

Hypertension

- Treat hypertension according to established guidelines.
- For guidelines on treatment holds, timing for restarting treatment or discontinuing treatment permanently, see Section 6.2.1, Table 2.

Wound Healing

- Treat wound according to established guidelines.
- For guidelines on treatment holds, timing for restarting treatment or discontinuing treatment permanently, see Section 6.2.1, Table 2.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

- Treat RPLS according to established guidelines.
- For guidelines on treatment holds, timing for restarting treatment or discontinuing treatment permanently, see Section 6.2.1, Table 2.

Arterial Thrombotic Events

- Initiate anticoagulation therapy.
- For guidelines on treatment holds, timing for restarting treatment or discontinuing treatment permanently, see Section 6.2.1, Table 2.

Pulmonary Embolism (PE) or Venous thromboembolism (VTE)

- Initiate anticoagulation therapy.
- For guidelines on treatment holds, timing for restarting treatment or discontinuing treatment permanently, see Section 6.2.1, Table 2.

Gastrointestinal Perforation or Fistula Formation

- Initiate treatment according to established guidelines.
- For guidelines on treatment holds, timing for restarting treatment or discontinuing treatment permanently, see Section 6.2.1, Table 2.

Bleeding

- Initiate treatment according to established guidelines.
- For guidelines on treatment holds, timing for restarting treatment or discontinuing treatment permanently, see Section 6.2.1, Table 2.

Hepatic Encephalopathy or Other Serious Signs of Liver Impairment

- Initiate treatment according to established guidelines.
- For guidelines on treatment holds, timing for restarting treatment or discontinuing treatment permanently, see Section 6.2.1, Table 2.

5.4.2. Suggested supportive care measures for the management of adverse events that are related to nivolumab

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent 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 the Nivolumab IB and in Appendix 1. The guidance provided in these algorithms should not replace the Investigator's medical judgment but should complement it.

5.5. Concomitant Medications

Although acetaminophen at doses of ≤ 2 grams/day is permitted, it should be used with caution in subjects with impaired liver function.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the sponsor-investigator by contacting the HCRN Project Manager. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.5.1. Permitted Concomitant Medications and Procedures

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care including transfusion of blood and blood products, treatment with antibiotics, analgesics, erythropoietin, or bisphosphonates, when appropriate. All concomitant medications will be recorded on the electronic case report form (eCRF).

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered beyond 30 days after the last dose of trial treatment should be recorded for SAEs as defined in Section 11.

Myeloid growth factors to treat subjects with neutropenia according to the American Society of Clinical Oncology (ASCO) Guidelines are permitted. Myeloid growth factors should be avoided (if medically appropriate) in Cycle 1 until subjects have developed a dose-limiting Grade 4 neutropenia.

Antiemetic agents may be administered at the discretion of the investigator but are not commonly required as a prophylactic agent. All other manifestations of the subject's malignancy should be treated at the discretion of the investigator.

Medications with potential central nervous system (CNS) effects are not prohibited in this study, but it is recommended that their use be minimized to avoid confusion in the interpretation of CNS effects should they occur during the course of treatment with ramucirumab and nivolumab.

In appropriate settings, such as combinations with agents known to produce frequent thrombocytopenia, restricted uses of anticoagulants should be considered.

All other medical conditions should be treated at the discretion of the investigator in accordance with local community standards of medical care.

5.5.2. Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy not specified in this protocol
- Immunotherapy not specified in this protocol
- Concomitant use of chemotherapy
- Investigational agents other than ramucirumab or nivolumab
- Radiation therapy
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids is allowed.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.6. Diet/Activity/Other Considerations

5.6.1. Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.6.2. Contraception

Ramucirumab and nivolumab may have adverse effects on the composition of sperm or on a fetus *in utero*. Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy, the potential of fetal toxicity occurring due to transmission of study drug, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

Women of childbearing potential (WOCBP) must be willing to use two methods of birth control. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. WOCBP should begin using birth control from the screening visit, throughout the study period, and up to 5 months following the last dose of study drugs. Total abstinence for the same study period is an acceptable alternative. Women of non childbearing potential or considered highly unlikely to conceive are defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is $\geq$ 45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study.

Men who are not surgically or medically sterile must agree to use an acceptable method of contraception. Male subjects with female sexual partners who are pregnant, possibly pregnant, or who could become pregnant during the study must agree to use condoms with spermicide from the date of the first dose of study drug, throughout the study period, and through 3 months after the last dose of study drug. Total abstinence for the same study period is an acceptable alternative.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medications may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, they must adhere to the contraception requirements described above. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.6.3. Use in Pregnancy

If a subject becomes pregnant while on study treatment, the subject will immediately be removed from the study treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to HCRN and to Eli Lilly and Company Global Patient Safety and Bristol-Myers Squibb (BMS) Global Pharmacovigilance & Epidemiology immediately and **within 24 hours** if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to HCRN. If a male subject impregnates his female partner, he must immediately inform the site study personnel and the pregnancy reported to HCRN and to Eli Lilly and Company and BMS Global Pharmacovigilance & Epidemiology, and followed as described above and in Section 11.

5.6.4. Use in Nursing Women

It is unknown whether ramucirumab or nivolumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

6. DOSE DELAYS AND MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4 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 Section 7. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring protocol therapy interruption or discontinuation at each study visit for the duration of their participation in the study.

Subjects discontinued from the treatment phase of the study for any reason will be evaluated 30 days (± 7) after the last dose of protocol therapy.

6.1 Discontinuation Information

If treatment with ramucirumab is unable to restart within 12 weeks of the planned treatment date, the subject will be permanently discontinued from ramucirumab.

NOTE: if either agent is permanently discontinued, treatment with the other agent may continue at the discretion of the investigator.

If treatment with nivolumab is unable to restart within 6 weeks of the planned treatment date, the subject will be permanently discontinued from nivolumab with the following exceptions:

- Dosing delays or interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Sponsor Investigator must be consulted.
- Dosing interruptions or delays lasting > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Sponsor Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Sponsor Investigator must be consulted.

6.2 Management of Infusion-Related Reaction/ Bronchospasm/ Hypersensitivity

NOTE: Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms of allergic-like reactions.

All Grade 3 or 4 infusion reactions from nivolumab should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE v4 guidelines.

Table 1A: Management of Infusion Related Reaction (IRR), Allergic Reaction, Hypersensitivity reaction or Bronchospasm from Nivolumab

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 nivolumab 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 will be permanently discontinued. Investigators should follow their institutional guidelines

Description	Action
	for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.
[1]For any ≤Grade 2 IRR, allergic reaction or bronchospasm, see Section 5.2 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).	

Table 1B: Management of Infusion Related Reaction (IRR), Allergic Reaction, Hypersensitivity Reaction or Bronchospasm from Ramucirumab.

Description	Action
CTCAE Grade 1 IRR, allergic reaction or bronchospasm[1]	Reduce the infusion rate by 50%.
CTCAE Grade 2 IRR, allergic reaction or bronchospasm[1]	Reduce the infusion rate by 50%.
Recurrent CTCAE Grade 2 IRR, allergic reaction or bronchospasm[1]	Stop the infusion. Administer additional doses of H1 and H2 blockers intravenously. Administer IV steroids and consider epinephrine and bronchodilators as clinically indicated.
CTCAE Grade 3 or 4 IRR, allergic reaction, bronchospasm or hypersensitivity reaction[2]	Will be permanently discontinued from ramucirumab.
[1]For any ≤Grade 2 IRR, allergic reaction or bronchospasm, see Section 5.2 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).	

An appropriate resuscitation plan should in place and a physician readily available during the period of drug administration. If treatment delay necessitates a period longer than 12 weeks for ramucirumab (or 6 weeks for nivolumab [see exceptions in Section 6]), treatment will be stopped and the subject permanently discontinued from the causative agent.

6.3 Dose Modifications

6.3.1 Ramucirumab Dose Modifications

Ramucirumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 2 below. See Section 5.4 for supportive care guidelines. **NOTE:** In addition to the guidelines below, subjects with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion.

Table 2: Ramucirumab dose modification guidelines for drug-related adverse events

Toxicity	Hold Treatment For	Timing for Restarting Treatment	Dose/rate reductions	Discontinue Subject
Proteinuria[1]	urine protein levels ≥2g/24hrs	once the urine protein level returns to < 2g/24hrs	Reduce dose to 6 mg/kg per dose for the first occurrence Reduce dose to 5 mg/kg for the second occurrence	For a third occurrence of >2g/24hrs, or if the protein level does not return to <2g/24hrs within 2 weeks
	urine protein level >3g/24hrs or in the setting of nephrotic syndrome	Permanently discontinue	Permanently discontinue	Permanently discontinue
Hypertension	Grade 3	Toxicity resolves to Grade 0-2 with medical management	No reduction if toxicity resolves	Permanently discontinue if medically significant hypertension cannot be controlled with antihypertensive therapy.
	Grade 4	Permanently discontinue	Permanently discontinue	Permanently discontinue
Wound healing complications	≥Grade 1; (NOTE: interrupt drug prior to any scheduled surgery)	Restart when wound is fully healed	No dose reductions warranted	Wound does not heal: permanently discontinue
Reversible posterior leukoencephalopathy syndrome (RPLS)[2]	Any occurrence	Permanently discontinue	Permanently discontinue	Permanently discontinue
Arterial thrombotic events[3]	Grade 3 or more severe	Permanently discontinue	Permanently discontinue	Permanently discontinue
Pulmonary embolism (PE) or Venous thromboembolism (VTE)[3]	Any event that occurs OR worsens despite anticoagulation therapy	Permanently discontinue	Permanently discontinue	Permanently discontinue
Venous thromboembolism (Subjects with unresected primary	Grade 3-4	When subject has begun anticoagulation	No dose reductions warranted	If in the opinion of the subject's physician, the tumor confers an

Toxicity	Hold Treatment For	Timing for Restarting Treatment	Dose/rate reductions	Discontinue Subject
tumors or local recurrence)[3]				excessive bleeding risk
Gastrointestinal perforation or fistula formation	Any occurrence	Permanently discontinue	Permanently discontinue	Permanently discontinue
Bleeding	Grade 3-4	Permanently discontinue	Permanently discontinue	Permanently discontinue
Hepatic encephalopathy or other serious signs of liver impairment	Any occurrence	Permanently discontinue	Permanently discontinue	Permanently discontinue
Infusion-related reactions	Grade 3-4	Permanently discontinue	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity	Grade 3 or severe	Toxicity resolves to Grade 0-1	No dose reductions warranted	Toxicity does not resolve within 12 weeks of last dose
	Grade 4[4]	Permanently discontinue	No dose reductions warranted	Permanently discontinue

[1] Proteinuria will be monitored by urine dipstick and/or urinary protein creatinine ratio for the development of worsening of proteinuria during ramucirumab therapy.
[2] All cases of RPLS must be reported via the SAE mechanism.
[3] Any venous or arterial event leading to discontinuation of ramucirumab therapy will be considered serious and should be reported via the serious adverse event (SAE) mechanism.
[4] The following events do not require discontinuation: lab alterations or Grade 4 fever.
NOTE: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

6.3.2 Nivolumab Dose Delay Criteria

Adverse events (both non-serious and serious) associated with nivolumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Nivolumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.4 for supportive care guidelines, including use of corticosteroids. **NOTE:** In addition to information in the table, permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event. Subjects with intolerable or persistent Grade 2 drug-related AE may have study medication held at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 6 weeks of the last dose unless delay beyond 6 weeks allows for prolonged steroid taper to manage toxicity. In such cases, the Sponsor Investigator must be consulted prior to re-initiating treatment.

Table 3: Nivolumab dose modification guidelines for drug-related adverse events

Toxicity	Hold Treatment For	Timing for Restarting Treatment	Discontinue Subject
Diarrhea/Colitis	Grade 2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose unless delay beyond 6 weeks allows for prolonged steroid taper to manage toxicity. In such cases, the Sponsor Investigator must be consulted prior to re-initiating treatment.
	Grade 4	Permanently discontinue	Permanently discontinue
Pneumonitis	Grade 2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose unless delay beyond 6 weeks allows for prolonged steroid taper to manage toxicity. In such cases, the Sponsor Investigator must be consulted prior to re-initiating treatment.
	Grade 3-4	Permanently discontinue	Permanently discontinue
Hepatitis	≥ Grade 2 if subject has baseline AST, ALT or total bilirubin that is within normal limits; ≥ Grade 3 if subject has baseline AST, ALT or total bilirubin within the Grade 1 toxicity range	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose unless delay beyond 6 weeks allows for prolonged steroid taper to manage toxicity. In such cases, the Sponsor Investigator must be consulted prior to re-initiating 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	Permanently discontinue	Permanently discontinue
Type I diabetes mellitus [TIDM] (if new onset) or Hyperglycemia	New onset T1DM or Grade 3 hyperglycemia	Toxicity resolves to Grade 0-1 even if requires physiologic hormone replacement	Resume nivolumab when subjects are clinically and metabolically stable.
	Grade 4	May need to permanently discontinue; see footnote #4	May need to permanently discontinue; see footnote #4
Hypophysitis	Grade 2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose unless delay beyond 6 weeks allows for prolonged steroid taper to manage toxicity. In such cases, the Sponsor Investigator must be consulted prior to re-initiating treatment.

Toxicity	Hold Treatment For	Timing for Restarting Treatment	Discontinue Subject
	Grade 4	Permanently discontinue	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 times the upper limit of normal	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose unless delay beyond 6 weeks allows for prolonged steroid taper to manage toxicity. In such cases, the Sponsor Investigator must be consulted prior to re-initiating treatment.
	Serum creatinine more than 6 times the upper limit of normal	Permanently discontinue	Permanently discontinue
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose unless delay beyond 6 weeks allows for prolonged steroid taper to manage toxicity. In such cases, the Sponsor Investigator must be consulted prior to re-initiating treatment.
	Grade 4 or confirmed SJS or TEN	Permanently discontinue	Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose unless delay beyond 6 weeks allows for prolonged steroid taper to manage toxicity. In such cases, the Sponsor Investigator must be consulted prior to re-initiating treatment.
	Immune-mediated encephalitis	Permanently discontinue	Permanently discontinue
Adrenal Insufficiency	Grade 2	Toxicity resolves to Grade 0-1 even if requires physiologic hormone replacement	Toxicity does not resolve within 12 weeks of last dose.
	Grade 3-4	May need to permanently discontinue; see footnote #4	May need to permanently discontinue; see footnote #4
Uveitis[1]	≥Grade 2	Permanently discontinue	Permanently discontinue
Thrombocytopenia	Grade 3 >7 days or associated with bleeding or Grade 4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity	Grade 2[2]	Toxicity resolves to Grade 0-1 even if requires physiologic hormone replacement for drug related endocrinopathy	Toxicity does not resolve within 6 weeks of last dose unless delay beyond 6 weeks allows for prolonged steroid taper to manage toxicity. In such cases, the Sponsor Investigator must be consulted

Toxicity	Hold Treatment For	Timing for Restarting Treatment	Discontinue Subject
			prior to re-initiating treatment.
	Grade 3 or severe	Toxicity resolves to Grade 0-1 even if requires physiologic hormone replacement for drug related endocrinopathy	Toxicity does not resolve within 6 weeks of last dose unless delay beyond 6 weeks allows for prolonged steroid taper to manage toxicity. In such cases, the Sponsor Investigator must be consulted prior to re-initiating treatment.
	Grade 4[4]	Permanently discontinue	Permanently discontinue

[1] Uveitis or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment

[2] Exceptions include grade 2 drug-related fatigue or laboratory abnormalities; do not delay for these events.

[3] Exceptions include grade 3 lymphopenia or leukopenia; do not delay for these events. In addition, any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The Investigator should be consulted for such Grade ≥ 3 amylase or lipase abnormalities.

[4] The following events do not require discontinuation:

- 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.
- Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Grade 4 lymphopenia or leucopenia
- Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Investigator.

NOTE: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.
Subjects with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects should be placed back on study therapy within 12 weeks of the scheduled interruption, unless otherwise discussed with the HCRN Project Manager. The reason for interruption should be documented in the subject's study record.

7 STUDY CALENDAR & EVALUATIONS

Study Day [Cycle = 14 days]	Screen	Cycle 1	Cycle 2 +	Safety Follow up[14]	Safety Follow up[14]	Long Term Follow Up[15]
	-28 days	Day 1 (± 3)	Day 1 (± 3)	30 days (±7)	90 days (±7)	Q 3 months (±14 days)
REQUIRED ASSESSMENTS						
Informed Consent/HIPAA auth.	X					
Medical History[1]	X					
Physical Exam	X	X	X	X		
Vital Signs including ECOG PS[2]	X	X	X	X		
AE Assessment and Con Meds	X	X	X	X	X	
LABORATORY ASSESSMENTS						
Blood Chemistries[3]	X	X[13]	X	X		
Thyroid Function Testing[4]	X	X[13]	X	X		
PT/INR and aPTT	X	X[13]	X	X		
Platelets, ANC & Hgb	X	X[13]	X	X		
Urinalysis	-7d[5]	X[13]	X			
Pregnancy Test for WOCP[6]	X	-24h	X[6]			
DISEASE ASSESSMENT						
CT or MRI chest, abdomen/pelvis[7]	X		X			X
CT or MRI Brain, if indicated[7]	[X]					
TREATMENT						
Nivolumab		X	X			
Ramucirumab		X	X			
CORRELATIVE STUDIES						
CT-guided biopsy[8]	X		X[8]			
Whole Blood for Somatic Baseline[9]		X				
Serum for soluble PD-L1 analysis[9]		X	C5D1			
BANKING SAMPLES						
Whole Blood[10] - Optional		X				
Serum and Plasma[11] - Optional		X		X		
Unstained Slides[12] - Optional		X	X[12]			
FOLLOW UP						
Survival status, additional cancer therapy						X

Footnotes:

1. Medical history to include demographics, prior treatments, radiation and surgical history. Other information obtained during the medical history includes: Smoking history to include: amount, frequency, start and stop dates of cigarette, cigar and pipe usage. A question about how the patient heard about the study. Prior genetic or biomarker testing results will be required if available.
2. Vital signs to include BP, HR, weight, height (screening) only. In addition, ECOG performance status should be obtained.
3. Blood Chemistries to include: sodium, potassium, blood urea nitrogen (BUN), serum creatinine (or GFR; see 3.1.7), calcium, albumin, ALT, AST, bilirubin, alkaline phosphatase (ALK), total protein, glucose.
4. Thyroid studies will be obtained every 3 cycles (about 6 weeks) starting with Cycle 4 (± 7 day window). The type of testing performed (TSH, T3 free vs direct, or T4 free vs direct) should be per local standards.
5. Within 1 week of study registration. If urine dipstick or routine analysis is ≥ 2+, a 24-hour urine collection for protein must demonstrate < 1000 mg of protein in 24 hours to allow participation in this protocol.
6. A negative serum or urine pregnancy test is required at screening for eligibility and within 24 hours of initiation of study treatment. If the urine test cannot be confirmed as negative, a serum pregnancy test will be required. Pregnancy testing will be done every 4 weeks.
7. Appropriate scans to assess disease status will be obtained within 4 weeks of initiation of study treatment including CT or MRI of the chest, abdomen/pelvis. After that time, disease assessment will be performed every 4 cycles (8 weeks) for 6 months, then every 6 cycles (12 weeks) until disease progression for a maximum of 2 years from initiation of study treatment. A brain MRI or CT will be performed at screening for subjects with a prior history of brain metastasis or if there is suspicion of brain metastatsis.
8. The subject will need to undergo a CT-guided biopsy (i.e., image-guided percutaneous lung biopsy) to obtain tumor tissue within 28 days before initiation of treatment and after 4 cycles (8 weeks) of treatment, for analysis of location and number of tumor infiltrating CD8+ cells and Granzyme B+ T cells, and PD-L1 and cytokine expression in different regions of the tumor. Biopsy to include FFPE and snap frozen tissue. See Correlative Laboratory Manual (CLM) for collection, labeling and shipping instructions.
9. Mandatory submission of whole blood for somatic baseline testing prior to treatment on C1D1. Mandatory submission of serum (soluble PD-L1) will be collected at Pre-Treatment Cycle 1 Day 1 and Pre-Treatment Cycle 5 Day 1. See CLM for collection, processing, labeling and shipping instructions.
10. Optional submission of whole blood for banking is to be collected at Pre-Treatment Cycle 1 Day 1. See CLM for collection, processing, labeling and shipping instructions.
11. Optional submission of serum and plasma for banking are to be collected at Pre-Treatment Cycle 1 Day 1 and at the D30 safety follow up visit. See CLM for collection, labeling, processing, and shipping instructions.
12. Optional submission of unstained slides for banking from the biopsy done prior to treatment C1D1 and after 4 cycles of treatment will be requested. See CLM for collection, labeling, and shipping instructions.
13. For Cycle 1 only: labs do not need to be repeated if done within 7 days of Day 1.
14. Safety Follow Up Visits: 30 days (±7) post last dose of study treatment. For subjects with unresolved treatment related toxicity, follow as medically appropriate until resolution or stabilization. Day 90 AE and conmed assessment may be done by phone, email or other avenues as appropriate.
15. Long-term follow up: Every 3 months until 2 years from initiation of study therapy. Follow up may be accomplished by phone call, email, local physician's record. Disease assessment will be performed per physcian's discretion. Results of all disease assessment should be captured. If the patient progresses, they should be followed for survival and/or initiation of anti-cancer therapy.

8 CRITERIA FOR DISEASE EVALUATION

A modified version of the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 will be used in this study [35]. For the purposes of this study, subjects will be reevaluated every 4 cycles (eight weeks) for 6 months, then every 6 cycles (12 weeks) until disease progression for a maximum of 2 years from initiation of study treatment. In addition to a baseline scan, confirmatory scans should also be obtained at least four weeks following initial documentation of objective response.

8.1 Target Lesions

All measurable lesions up to a maximum of 5 lesions representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). Measurable lesions are defined as those that can be accurately measured in at least one dimension as 10 mm with CT scan. A lymph node must be 15 mm in short axis by CT scan in order to be considered pathologically enlarged and measurable. All measurements must be recorded in millimeters. A sum of the diameters (long diameter (LD) for all non-nodal target lesions and short axis for nodal lesions) will be calculated and reported as the baseline sum LD. The baseline sum of all diameters will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

In subjects with pleural mesothelioma the typical mesothelial “rind” should be measured on 3 separate levels at least 2 cm apart, perpendicularly from the chest wall on a given cut. Each level should be measured in two different places. The three rind thicknesses should be recorded for a given level and compared on subsequent scans. Clear anatomic landmarks should be recorded carefully to ensure consistency from scan to scan. At least one level should have a measurement $\geq$ 1.5 cm. Pleural areas where the initial thickness is less than 1 cm should not be used as evaluation measurement.

A sum of the measurements of the pleural rind obtained at 3 different levels should be calculated and reported as the baseline sum LD.

These modified RECIST 1.1 criteria have been previously validated in patients with mesothelioma [35]. Response assessment using these methods has been found to be a greater clinical predictor for survival in patients with mesothelioma than a method of longest diameter to assess pleural thickness.

8.1.1 Complete Response (CR)

Disappearance of all target lesions. Changes in tumor measurements must be confirmed by repeat studies performed no less than 4 weeks after the criteria for response are first met.

8.1.2 Partial Response (PR)

At least a 30% decrease in the sum of the diameters of target lesions taking as reference the baseline sum LD. Changes in tumor measurements must be confirmed by repeat studies performed no less than 4 weeks after the criteria for response are first met.

8.1.3 Progression
At least a 20% increase in the sum of the diameters of target lesions taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.

8.1.4 Stable Disease (SD)
Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of the diameters since the treatment started. Subjects having a documented response with no reconfirmation of the response will be listed with stable disease.

8.2 Non-target Lesions
All other lesions (or sites of disease) not included in the "target disease" definition should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent."

8.2.1 Complete Response (CR)
Disappearance of all non-target lesions and normalization of tumor marker level. If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

8.2.2 Non-complete Response (non-CR)/ Non-progression (non-PD)
Persistence of one or more non-target lesion and/or maintenance of tumor marker level above the upper limits of normal.

8.2.3 Progression (PD)
Appearance of one or more new lesions. Unequivocal progression of existing non-target lesions. Although a clear progression of non-target lesions is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the study chair.

8.3 Evaluation of Best Overall Response
The best overall response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesion	Overall response
CR	CR	No	CR
CR	Non-CR/PD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

NOTE:

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
- Conditions that may define early death include subjects that have died without documentation of disease progression and before it was time to conduct the first tumor reassessment. Inevaluable subjects are defined as not having received protocol treatment (regardless of how much was received) and no follow-up assessment completed before initiation of alternative treatment.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

8.4 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

- Clinical Lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

- Chest X-ray: Lesions on chest X-ray are not acceptable as measurable lesions. A CT scan of the chest (with abdomen and pelvis if needed) must be used to evaluate measurable disease in this trial. For pelvic and/or abdominal lesions an MRI may be used to evaluate measurable disease. The imaging modality used to determine the initial measurement should continue to be used consistently for subsequent measurement evaluations.

- Conventional CT of the chest should be performed with contrast if possible and with cuts of 2.5 mm in slice thickness contiguously. Spiral CT is preferred. CT scans of the abdomen, and pelvis may also be performed using standard slice thickness (5 mm).

- Endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained.

8.5 Confirmation Measurement/Duration of Response

8.5.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies that should be performed no less than four weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after initiation of study treatment at a minimum interval of six to eight weeks.

8.5.2 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

8.5.3 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

9 BIOLOGICAL CORRELATIVES

Any leftover samples after initial testing is complete will be kept for future unspecified cancer related research. Permission from the subject will be obtained for storage of these samples via informed consent.

9.1 Correlate PD-L1 expression in tumor tissue (from biopsy before treatment) with best clinical response (modified RECIST 1.1 criteria) in subjects with previously-treated mesothelioma. (mandatory)

Expression and localization (central versus peripheral) of PD-L1 in tumor tissue obtained by CT-guided biopsies (i.e., image-guided percutaneous lung biopsy) will be determined by IHC and will be correlated with clinical outcome assessed by imaging. Unstained slides are to be submitted; a tumor block is not acceptable. A needle aspirate, frozen sample, plastic embedded sample, cell block, clot, bone, bone marrow or cytologic specimen are not acceptable for PD-L1 analyses. Refer to the CLM for collection, labeling and shipping instructions.

9.2 Correlate change in PD-L1 expression in tumor tissue from before therapy (assessed within 14 days before treatment) to after 4 cycles (8 weeks) of therapy with best clinical response (modified RECIST 1.1 criteria) at the end of Cycle 4 (Week 8) in subjects with previously-treated mesothelioma.

Expression and localization (central versus peripheral) of PD-L1 in tumor tissue obtained by CT-guided biopsies (i.e., image-guided percutaneous lung biopsy) will be determined by IHC and will be correlated with clinical outcome assessed by imaging. Unstained slides are to be submitted; a tumor block is not acceptable. A needle aspirate, frozen sample, plastic embedded sample, cell block, clot, bone, bone marrow or cytologic specimen are not acceptable for PD-L1 analyses. Refer to the CLM for collection, labeling and shipping instructions.

9.3 Correlate cytokine genes expressions and change in tumor tissue (such as IL-1, IL-2, IL-6, GM-CSF, IL-10, IL-12, T-bet, IRF1, IFNγ, CXCL1, CXCL9, CXCL10, CCL2 and 5) (from biopsy before and during treatment) with best clinical response (modified RECIST 1.1 criteria) at the end of Cycle 4 (Week 8) in subjects with previously-treated mesothelioma. (mandatory)

Expression and localization (central versus peripheral) of cytokines in tumor tissue obtained by CT-guided biopsies (i.e., image-guided percutaneous lung biopsy) will be determined by nanostring or comparable technology. Biopsy to include FFPE and snap frozen tissue. Refer to the CLM for collection, labeling and shipping instructions.

9.4 Correlate change in soluble PD-L1 level in serum during therapy (assessed pre-dose Cycles 1 and 5), to the best clinical response (modified RECIST 1.1 criteria) at the end of Cycle 4 (Week 8) in subjects with previously-treated mesothelioma. (mandatory)

Whole blood for serum submission will be collected predose on Cycle 1 Day 1 and Cycle 5 Day 1 for analysis of soluble PD-L1 levels. Change in soluble PD-L1 levels as a result of treatment will be examined in relation to the best clinical response (modified RECIST 1.1 criteria [35]) at the end of Week 4 (Cycle 8). This analysis determined by ELISA assay or comparable technology will be conducted by a lab such as Martell Diagnostic Laboratory, at Roseville, MN. Refer to the CLM for collection, processing, labeling and shipping instructions.

9.5 Correlate change in number of CD8+ cells and Granzyme B+ T cells in tumor tissue from before therapy (assessed within 14 days before treatment) to after 4 cycles (8 weeks) of therapy to the best clinical response (modified RECIST 1.1 criteria) at the end of Cycle 4 (Week 8) in subjects with previously-treated mesothelioma. (mandatory)

Number and localization (central versus peripheral) of CD8+ cells and Granzyme B+ T cells in tumor tissue obtained by CT-guided biopsies (i.e., image-guided percutaneous lung biopsy) will be determined by IHC by a lab such as Biothera Pharmaceuticals, Inc. (Eagan, MN) and will be correlated with clinical outcome assessed by imaging. Changes in number of CD8+ cells and Granzyme B+ T cells from before therapy (assessed within 14 days before treatment) to after 4 cycles (8 weeks) of therapy will be examined in relation to the best clinical response (modified RECIST 1.1 criteria [35]) at the end of Cycle 4 (Week 8). Other markers such as but not limited to CD4 FoxP3, PD-L1, Pan-cytokeratin, and DAPI. This analysis determined by ELISA assay or comparable technology will be conducted by a lab such as Biothera Pharmaceuticals, Inc. (Eagan, MN). Refer to the CLM for collection, processing, labeling and shipping instructions.

9.6 Samples for future studies (optional)

Subject consent will be obtained for additional samples collected for future unspecified cancer related research. HCRN will manage the banked samples. Samples will be banked indefinitely in the HCRN Biorepository. Please refer to the CLM for all sample collection, processing, labeling, and shipping instructions.

This includes:

- Whole blood: Optional - Whole blood will be collected prior to treatment on C1D1.
- Pre- and Post-treatment plasma: Optional - Whole blood for plasma will be collected prior to treatment on Cycle 1 Day 1 and at the D30 safety visit.
- Pre- and Post-treatment serum: Optional - Whole blood for serum will be collected prior to treatment on Cycle 1 Day 1 and at the D30 safety visit.
- Pre- and Post-treatment biopsies: Optional - Unstained slides will be collected prior to treatment on Cycle 1 Day 1 and post Cycle 4.

10 DRUG INFORMATION

10.1 Drug Name: Cyramza® (Ramucirumab; IMC-1121B [Anti-VEGFR2 antibody])

10.1.1 Chemical name and properties

Disulfide with human monoclonal IMC-1121B κ-chain anti-(human vascular endothelial growth factor receptor type VEGFR-2 extracellular domain) (human monoclonal IMC-1121B γ-chain) immunoglobulin G1, dimer. Ramucirumab is a recombinant human IgG1 monoclonal antibody that specifically binds to vascular endothelial growth factor receptor 2.

10.1.2 Availability

Eli Lilly and Co. will provide ramucirumab 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.

10.1.3 Storage

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Unopened vials of ramucirumab are stable until the expiration date indicated on the package when stored at 2° to 8ºC (36° to 46ºF). Keep the vial in the outer carton in order to protect from light. Do not freeze or shake. Store diluted infusion for no more than 24 hours at 2°C to 8°C (36°F to 46°F) or 4 hours at room temperature (below 25°C [77°F]).

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

10.1.4 Dosage and Administration

Eli Lilly and Company will supply ramucirumab directly to sites at no cost to subjects in this clinical trial. Ramucirumab is supplied in a sterile form for intravenous use only. Ramucirumab is a sterile, preservative-free, clear to slightly opalescent and colorless to slightly yellow solution for intravenous infusion following dilution and preparation. Ramucirumab is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-dose vials. CYRAMZA is formulated in glycine (9.98 mg/mL), histidine (0.65 mg/mL), histidine

monohydrochloride (1.22 mg/mL), polysorbate 80 (0.1 mg/mL), sodium chloride (4.383 mg/mL), and Water for Injection, USP, pH 6.0.

Inspect vial contents for particulate matter and discoloration prior to dilution. Discard the vial, if particulate matter or discolorations are identified. Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use. Keep the vial in the outer carton in order to protect from light.

- Calculate the dose and the required volume of ramucirumab needed to prepare the infusion solution. The dosing calculations should be based on the actual body weight at baseline. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the original dose, the dose must be recalculated. All doses should be rounded to the nearest milligram. Vials contain either 100 mg/10 mL or 500 mg/50 mL at a concentration of 10 mg/mL solution of ramucirumab.
    - Withdraw the required volume of ramucirumab and further dilute with only 0.9% Sodium Chloride Injection in an intravenous infusion container to a final volume of 250 mL. Do not use dextrose containing solutions.
    - Gently invert the container to ensure adequate mixing.
    - DO NOT FREEZE OR SHAKE the infusion solution. DO NOT dilute with other solutions or co-infuse with other electrolytes or medications.
    - Store diluted infusion for no more than 24 hours at 2°C to 8°C (36°F to 46°F) or 4 hours at room temperature (below 25°C [77°F]).
    - Discard vial with any unused portion of ramucirumab.

10.1.5 Side Effects

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

Ramucirumab is generally well tolerated and demonstrates a favorable safety profile in comparison to traditional chemotherapy. Important identified risks for ramucirumab include, but are not limited to hypertension, proteinuria/nephrotic syndrome, arterial thrombotic events, impaired wound healing, infusion related reactions, hemorrhage, reversible posterior leukoencephalopathy syndrome, thyroid dysfunction, and gastrointestinal disorders (perforation/diarrhea).

Further details around frequency, reporting, and management of adverse events can be found in the current version of the Investigator's Brochure.

10.2 Drug Name: Opdivo® (Nivolumab; [Anti-PD-1 Antibody])

10.2.1 Other names and properties

ONO-4538, MDX-1106, BMS-936558-01 or BMS-936558, anti-PD-1, anti-programmed cell death-1 monoclonal antibody

10.2.2 Availability

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

10.2.3 Product Description and Dosage Form

Nivolumab Injection, 100 mg/10 mL (10 mg/mL),

Nivolumab Injection, 100mg/10 mL (10mg/mL) is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentaacetic acid (pentetic acid), and polysorbate 80 (Tween™ 80), pH 6.0 and includes an overfill to account for vial, needle, and syringe holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals. The only difference between the two drug product presentations is the vial fill volume.

10.2.4 Storage

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."

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

10.2.5 Dosage and Administration

The safety and efficacy of 240 mg Q2W flat dose of nivolumab is expected to be similar to 3 mg/kg Q2W dosing regimen. A flat dose of nivolumab 240 mg Q2W was selected since it is identical to a dose of 3 mg/kg for subjects weighing 80 kg, the observed median body weight in nivolumab treated cancer patients. Using a population pharmacokinetics model, the overall distributions of nivolumab exposures (Cavgss, Cminss, Cmaxss, and Cmin1) are comparable after treatment with either 3 mg/kg or 240 mg nivolumab. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of 240 mg flat dose compared to 3 mg/kg Q2W regimen, it is expected that the safety and efficacy profile of 240 mg Q2W nivolumab will be similar to that of 3 mg/kg nivolumab.

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. When the dose is fixed (eg, 240 mg, 360 mg or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 120 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.

10.2.6 Storage and Stability

Nivolumab Injection, 100 mg/10 mL (10 mg/mL)
Vials of nivolumab injection must be stored at 2° to 8°C (36° to 46°F) and protected from light and freezing.

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.

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

10.2.7 Handling and Disposal

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

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

10.2.8 Dispensing

Nivolumab must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. 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.

10.2.9 Side Effects

Please refer to the nivolumab package insert 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 the Nivolumab IB and in Appendix 1.

The overall safety experience with nivolumab is based on experience in approximately 12,300 subjects 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. The most frequently reported treatment-related AE is fatigue, which is almost always of low grade.

Most related AEs are thought to be due to the effects of inflammatory cells on specific tissues. A variety of preferred terms (PTs) have been used to describe similar kinds of organ-related AEs,

with the result being that AE frequency tables organized by PTs can lead to underestimation of the frequency of similar kinds of organ-related AEs. Select AE categories group together the most common and impactful PTs by organ category. These categories include the following: pulmonary, GI, hepatic, skin, endocrine, hypersensitivity/infusion reaction, and renal AEs.

Pulmonary Adverse Events

Pulmonary AEs have been observed following treatment with nivolumab. The frequency of pulmonary AEs may be greater with nivolumab combination therapies than with nivolumab monotherapy. The majority of cases reported were Grade 1 or 2, and subjects presented with either asymptomatic radiographic changes (e.g., focal ground glass opacities and patchy infiltrates) or with symptoms of dyspnea, cough, or fever. Subjects with reported Grade 3 or 4 pulmonary AEs were noted to have more severe symptoms, more extensive radiographic findings, and hypoxia. Pulmonary AEs have been reported in subjects with a variety of tumor types; however, there have been numerically more cases in subjects with NSCLC. It is not clear whether the underlying NSCLC is a distinct risk factor, or if subjects with NSCLC are more likely to develop radiographic changes and symptoms for which it is difficult to distinguish between nivolumab-related and unrelated causes. At this time, no other underlying risk factor, including prior radiotherapy, presence of lung metastases, or underlying pulmonary medical history, has yet to be identified.

Gastrointestinal Adverse Events

Gastrointestinal AEs have been observed following treatment with nivolumab. Most cases of diarrhea were of low grade (Grade 1-2). Colitis occurred less frequently than diarrhea. High-grade cases of diarrhea and colitis were managed with corticosteroids and, in all cases, the events resolved.

Diverticular Perforation

The prevalence of diverticulosis in the general population is common and increases with age from 10% under 40 years of age to approximately 50% over 60 years of age. Approximately 10% to 25% of subjects with diverticulosis develop diverticulitis. Perforation occurs in 50% to 70% of instances of complicated diverticulitis [36, 37]. Corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and opioid analgesics are known risk factors for diverticular perforation [38]. Given the high prevalence of diverticulosis and diverticulitis in the general population, it is expected that some nivolumab-treated subjects will have these conditions concurrently with their malignancy. Cases of diverticular perforation while on concomitant corticosteroids (6 cases) or NSAID (1 case) were observed in nivolumab program. While there is insufficient evidence to suggest that diverticulosis or diverticulitis is a predisposing factor for GI perforation following nivolumab administration, clinical caution should be exercised, as appropriate, for subjects on concomitant medications of corticosteroids, NSAID, or opioid analgesics. In addition, be vigilant for signs and symptoms of potential perforation, especially in subjects with known diverticular disease.

Hepatic Adverse Events

Hepatic AEs, including elevated liver function tests (LFTs) and, infrequently, drug-induced liver injury (DILI) have been observed following treatment with nivolumab and nivolumab in combination with ipilimumab. Most cases were of low or moderate grade. Higher-grade hepatic

AEs, including DILI, were managed with corticosteroids (with or without mycophenolate mofetil) and, in almost all cases, the events resolved.

Endocrinopathies

Endocrinopathies have been observed following treatment with nivolumab. Most cases were of low or moderate grade. The events have typically been identified through either routine periodic monitoring of specific laboratories (e.g., TSH) or as part of a work-up for associated symptoms (e.g., fatigue). Events may occur within weeks of beginning treatment, but also have been noted to occur after many months (while still on treatment). More than 1 endocrine organ may be involved (e.g., hypophysitis [pituitary inflammation] may need to be evaluated at the time adrenal insufficiency or thyroid disorder is suspected). Moderate- to high-grade cases were managed with hormone replacement therapy and, in some cases, with the addition of corticosteroids. In some cases, nivolumab treatment was held until adequate hormone replacement was provided.

Skin Adverse Events

Rash and pruritus were the most common skin AEs observed following treatment with nivolumab. The rash was typically focal with a maculopapular appearance occurring on the trunk, back, or extremities. Most cases have been of low or moderate grade. In some cases, rash and pruritus resolved without intervention. Topical corticosteroids have been used for some cases of rash. Anti-histamines have been used for some cases of pruritus. More severe cases responded to systemic corticosteroids.

Renal Adverse Events

Elevated creatinine and biopsy-confirmed tubulointerstitial nephritis and allergic nephritis have been infrequently observed following treatment with nivolumab. The frequency of renal AEs may be greater with nivolumab combination therapies than with nivolumab monotherapy. Most cases were Grade 2 or 3 and based on creatinine elevation. Subjects with a history of renal cell carcinoma or prior nephrectomy did not appear to be at higher risk. Events were managed with corticosteroids and, in all cases, renal function partially or fully improved.

Neurologic Adverse Events

Neurologic AEs have been uncommonly observed following treatment with nivolumab. The frequency of neurologic AEs may be greater with nivolumab + ipilimumab combination therapies than with nivolumab monotherapy or other nivolumab combinations. Neurologic AEs can manifest as central abnormalities (e.g., aseptic meningitis, encephalopathy, or encephalitis) or peripheral sensory/motor neuropathies (e.g., Guillain-Barre Syndrome, myasthenia gravis complicated with sepsis and fatality). The onset has been observed as early as after a single treatment with the nivolumab + ipilimumab combination.

Infusion Reactions

Infusion reactions, including high-grade hypersensitivity reactions, following administration of nivolumab are uncommon. Investigators are advised to monitor for fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty in breathing during and immediately after administration of nivolumab.

Lipase/Amylase Elevations
Asymptomatic elevations in lipase and amylase have been reported. In monotherapy studies, lipase and amylase levels were not systematically monitored, so an estimate of the frequency of asymptomatic lipase/amylase elevations is unknown. In studies evaluating the safety of the nivolumab + ipilimumab combination in multiple tumor types, lipase and amylase levels were systematically monitored, and elevations in any grade of lipase/amylase were consistently noted in approximately 10% to 30% of subjects. Very few subjects reported associated symptoms (e.g., abdominal pain) or radiographic findings (e.g., stranding) consistent with pancreatitis. Thus, there does not seem to be clinical significance to the elevated laboratory values.

Uveitis and Visual Complaints
Immune therapies have been uncommonly associated with visual complaints. Inflammation of components within the eye (e.g., uveitis) is an uncommon, but clinically important, event. Uveitis may occur more frequently with nivolumab + ipilimumab combination therapy than with nivolumab monotherapy or nivolumab in combination with other therapies. An ophthalmologist should evaluate visual complaints with examination of the conjunctiva, anterior and posterior chambers, and retina. Topical corticosteroids may be used to manage low-grade events. Low-grade events that do not resolve and high-grade events should be managed with systemic corticosteroids. Consultation with a BMS medical monitor should be sought for all cases of ocular inflammatory events. Complaints of double vision should also prompt medical evaluation. In addition to ocular inflammatory events, a work-up should also consider pituitary inflammation as a cause

Other Immune-mediated Adverse Events
For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids administered. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.

10.3 Overlapping Toxicities of Ramucirumab and Nivolumab
Overlapping toxicities of the study medications include: renal failure, infusion reaction, fatigue, decreased appetite and headache.

11 ADVERSE EVENTS

11.1 Definitions of Adverse Events

11.1.1 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

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.

11.1.2 Laboratory Test Abnormalities

However, the following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE or Drug Induced Liver Injury (DILI)
- any laboratory abnormality that required the participant to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

Wherever possible, the clinical rather than laboratory term should be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

11.1.3 Serious Adverse Event (SAE)

An SAE is an adverse event that:

- Results in death. **NOTE:** Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- 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.
    - Potential drug induced liver injury (DILI) is also considered an important medical event.
    - Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.

- Although pregnancy is not always serious by regulatory definition, it must be handled as an SAE.
- Ramucirumab and/or nivolumab overdose. For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for ramucirumab and/or nivolumab by 20%.
- Any venous or arterial event leading to discontinuation of ramucirumab therapy will be considered serious and should be reported per SAE guidelines.
- Cases of RPLS must be reported per SAE guidelines.

11.1.4 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.

11.1.5 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)

11.2 Adverse Event (AE) Recording

- Adverse events (AEs) will be recorded from the time of consent until 100 days after treatment discontinuation of study drugs, or until a new anti-cancer treatment starts, whichever occurs first.
- AEs will be recorded regardless of whether or not the event(s) are considered related to the study drugs.
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All AEs considered related to study drugs will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is occurs first.

11.3 Serious Adverse Event (SAE) Reporting

11.3.1 Site Requirements for Reporting SAEs to HCRN

- SAEs will be reported from time of signed informed consent until **100** days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- SAEs 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 will be reported whether or not they are related to the study drug(s).
- All SAEs 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 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.

Additionally, any serious adverse event, considered by an investigator to be related to either study drug, which is brought to the attention of the investigator at any time outside of the 100-day time period specified above, also must be reported immediately to HCRN.

The site will submit the completed SAE Submission Form to HCRN **within 1 business day** of discovery of the event. The form may be sent electronically to safety@hoosiercancer.org. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements. The original copy of the SAE Submission Form and the email correspondence must be kept within the study file at the study site.

Once the SAE has resolved, sites must submit a follow up SAE Submission Form within a reasonable timeframe to HCRN electronically to safety@hoosiercancer.org.

11.3.2 HCRN Requirements for Reporting SAEs to Eli Lilly

HCRN will submit all at least possibly related SAEs (including DILI, overdose, pregnancy, etc.) received from sites to Eli Lilly **within 7 business day** of receipt of the SAE Reporting Form and to regulatory authorities (FDA) per federal guidelines.

HCRN will fax or email a SAE Submission Form for all SAE reports and any other relevant safety information to Eli Lilly and Company (Attn: Global Patient Safety; FAX 866-644-1697 or 317-453-3402)

HCRN will provide follow-up information to Eli Lilly and Company Global Patient Safety as reasonably requested.

11.3.3 HCRN Requirements for Reporting SAEs to BMS

HCRN will submit all SAEs (including DILI, overdose, pregnancy, etc.) received from sites to BMS **within 1 business day** of receipt of the SAE Reporting Form and to regulatory authorities (FDA) per federal guidelines.

HCRN will fax or email a SAE Submission Form for all SAE reports and any other relevant safety information to BMS (Attn: Global Pharmacovigilance & Epidemiology; email: Worldwide.Safety@BMS.com; FAX: 609-818-3804).

HCRN will provide follow-up information to BMS Global Pharmacovigilance & Epidemiology as reasonably requested.

11.3.4 Reporting of Pregnancy

It is the responsibility of site investigators or their designees to report any pregnancy in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 5 months)following the last dose of study drugs for females, and 7 months following the last dose of study drugs for males.. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported **within 1 business day** to HCRN. HCRN will report the event **within 1 business day** to Eli Lilly and Company (Attn: Global Patient Safety; FAX 866-644-1697 or 317-453-3402) and BMS (Attn: Global Pharmacovigilance & Epidemiology; Worldwide.Safety@BMS.com; FAX: 609-818-3804).

11.3.5 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as:

1. An elevated AST or ALT lab value that is greater than 3 × the upper limit of normal, **and,**
2. an elevated total bilirubin lab value that is greater than 2 × the upper limit of normal without initial findings of cholestasis (elevated serum alkaline phosphatase), **and**,
3. No other immediately apparent possible causes of aminotransferase (ALT or AST) elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

DILIs that occur in any subject from the date of first dose through 100 days following discontinuation of dosing, whether or not related to Eli Lilly and Company's product and/or BMS's product, must be reported **within 1 business day** to HCRN. The site will submit a completed SAE Submission Form to HCRN **within 1 business day** of discovery of the event. The form may be sent electronically to safety@hoosiercancer.org.

HCRN will report the event **within 1 business day** to Eli Lilly and Company (Attn: Global Patient Safety; FAX 866-644-1697 or 317-453-3402) and BMS (Attn: Global Pharmacovigilance & Epidemiology; Worldwide.Safety@BMS.com; FAX: 609-818-3804).

11.3 Sponsor-Investigator Responsibilities

HCRN 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.

11.4 HCRN Responsibilities for Reporting SAEs to the FDA

11.4.1 Protocols Conducted Under an IND

HCRN has been designated to manage the Investigational New Drug Application (IND) associated with this protocol on behalf of the sponsor-investigator. HCRN will cross-reference this submission to Eli Lilly's and BMS's parent INDs at the time of submission. Additionally, HCRN will submit a copy of these documents to Eli Lilly and BMS at the time of submission to FDA.

HCRN 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, HCRN will submit a copy of these reports to Eli Lilly and BMS at the time of submission to FDA.

11.5 IND Safety Reports Unrelated to This Trial

Eli Lilly and Company and BMS will provide HCRN with IND safety reports from external studies that involve the study drugs to HCRN (safety@hoosiercancer.org) per their guidelines. HCRN 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. HCRN 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 HCRN, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

12 STATISTICAL CONSIDERATIONS

12.1 Study Design

The primary objective of this study is to evaluate the response rate of checkpoint inhibitor with combination of the anti PD-1 agent, nivolumab and the anti VEGFR2 antibody, ramucirumab in subjects with previously-treated mesothelioma. The primary study endpoint is the response rate [complete response (CR) + partial response (PR)] of patients to this treatment. Nivolumab and ramucirumab will be given on Day 1 of each 14-day cycle. Treatment will continue up to 24 months (52 cycles) or until disease progression, unacceptable toxicity, subject refusal, or subject death. Subjects who voluntarily stop the study, have progressive disease, or unacceptable toxicities will be followed for a total of 24 months after initiation of study treatment.

Correlative research analyses include examining the relationship between best clinical response overall with tissue PD-L1, and at the end of Cycle 4 (Week 8) with changes in PD-L1 and cytokine genes expressions and number of CD8+ and Granzyme B+ T cells in tumor tissue from before therapy to the end of Cycle 4 (Week 8). Research analyses also include examining the relationship between changes in soluble PD-L1 level, during therapy (assessed pre-dose Cycles 1 and 5 [(Days 1 and 57 of treatment period, respectively]) relative to baseline to the best clinical response (modified RECIST 1.1 criteria) and to treatment outcome.

12.2 Criteria for Stopping Study

The study will be stopped for safety reasons if ≥ 2 subjects in first 20 or ≥ 3 in first 30 subjects develop grade 5 therapy related toxicity during first 4 cycles of therapy.

12.3 Sample Size

This is a non-randomized one arm study of nivolumab and ramucirumab. The primary study endpoint is the response rate [complete response (CR) + partial response (PR)] of patients for the therapy. Previous studies identified such response rate of 20% [Alley's Lancet Oncology paper 2017]. We hypothesize a response rate of 40%. Controlling for a probability of Type I error at 0.05 (one-sided), our sample size is estimated to be 33 to ensure 80% statistical power in successfully detecting an alternative response rate of 0.40, compared to a null rate of 0.2. With estimated up to 5% of patients that are not evaluable for primary endpoint, sample size will be increased to 35. Sample size analyses were conducted using the PASS software (NCSS, Kaysville, Utah, USA).

12.4 Analysis of Primary Objectives/Aims

The primary endpoint is determination of the response rate [complete response (CR) + partial response (PR)] with the combination of the anti PD-1 agent, nivolumab and the anti VEGFR2 antibody, ramucirumab in subjects with previously-treated mesothelioma; it will be calculated with associated 95% confidence interval using.

12.5 Analysis of Secondary Endpoints

Characterize adverse effects (AE) of nivolumab in combination with ramucirumab in subjects with previously-treated mesothelioma.

Proportion of subjects with each grade of adverse events as defined by CTCAE v4 will be computed along with 95% confidence intervals, and reported in a tabular and descriptive manner.

Median progression free survival (PFS) and overall survival (OS) times will be computed, and PFS rates at 3, 6, and 12 months and OS rates at 2 years +/- 2 months will be calculated with associated 95% confidence intervals. Kaplan-Meier curves for reach survival rate will be plotted.

12.6 Analysis of Correlative Endpoints

- PD-L1 expression in tumor tissue (categorical based on 5% threshold) from before therapy (assessed within 14 days before treatment) will be correlated with the best clinical response (modified version of RECIST 1.1) and treatment outcome. Chi-square statistics will be computed.

- Change in PD-L1 expression in tumor tissue from before therapy (assessed within 14 days before treatment) to after 4 cycles (8 weeks) of therapy will be correlated with the best clinical response (modified version of RECIST 1.1) and treatment outcome. Chis-square statistics will be computed.

- Change in cytokine expression in tumor tissue from before therapy (assessed within 14 days before treatment) to after 4 cycles (8 weeks) of therapy will be correlated with the best clinical response (modified version of RECIST 1.1) and treatment outcome. Chi-square statistics will be computed.

- Change in soluble PD-L1 level during therapy (assessed pre-dose Cycles 1 and 5 [(Days 1 and 57 of treatment period, respectively]) relative to baseline will be examined in relation to the best clinical response (modified version of RECIST 1.1) and treatment outcome. Correlation-statistics will be computed.

- Change in number of CD8+ cells (rich vs. poor) and Granzyme B+ T cells (rich vs. poor) from before therapy (assessed within 14 days before treatment) to after 4 cycles (8 weeks) of therapy will be examined in relation to the best clinical response (modified version of RECIST 1.1) and treatment outcome. Chi-square statistics will be computed.

13 TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Board (DSMB)

This study will have a Data and Safety Monitoring Board (DSMB). The DSMB is chaired by an independent medical oncologist external to this trial. The DSMB will provide a recommendation to the sponsor-investigator after all information is reviewed. This information will also be provided to HCRN who will distribute to the site investigator/participating sites for submission to their respective IRB, according to the local IRB's policies and procedures.

The DSMB review will include but is not limited to:

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

The DSMB will review data a minimum of twice per year during the active study drug administration phase of the study.

13.2 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. Automated edit check listings will be used to generate queries in the EDC system and transmitted to the site to address in a timely fashion. 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. 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 HCRN or its designee.

The trial site may also be subject to quality assurance audit by Eli Lilly, BMS, or their designees as well as inspection by appropriate regulatory agencies.

13.3 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 HCRN 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 DATA HANDLING AND RECORD KEEPING

14.1 Data Management

HCRN will serve as the Clinical Research Organization for this trial. Data will be collected through the web-based clinical research platform, a system compliant with Good Clinical Practices and Federal Rules and Regulations. HCRN 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.

14.2 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.

The completed dataset is housed at HCRN 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 HCRN. After the initial publication, the complete data set will be available to all HCRN institutions.

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/HCRN, the investigator agrees to keep records, including the identity of all participating 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. To comply with international regulations, the records should be retained by the investigator in compliance with regulations. No records will be destroyed until HCRN confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subject 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 team. Samples that are collected will be identified by a subject study number assigned at the time of registration to the trial.

Subjects will be informed in writing that some organizations, including the sponsor-investigator and his/her research associates, HCRN, Eli Lilly and Company, 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 subject's identity will remain confidential.

15 ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol, including the final version of the informed consent form must be approved in writing by an IRB. The investigator must submit written approval to the HCRN office before he or she can enroll any 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 annually, as local regulations require.

Progress reports and notifications of serious unexpected adverse drug reactions will be provided to the IRB according to local regulations and guidelines.

15.2 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.

15.3 Informed Consent Process

The 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 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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17 APPENDIX 1: Nivolumab Management Algorithms

These general guidelines constitute guidance to the site Investigator and may be supplemented through discussions with the Sponsor-Investigator by contacting the HCRN 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.

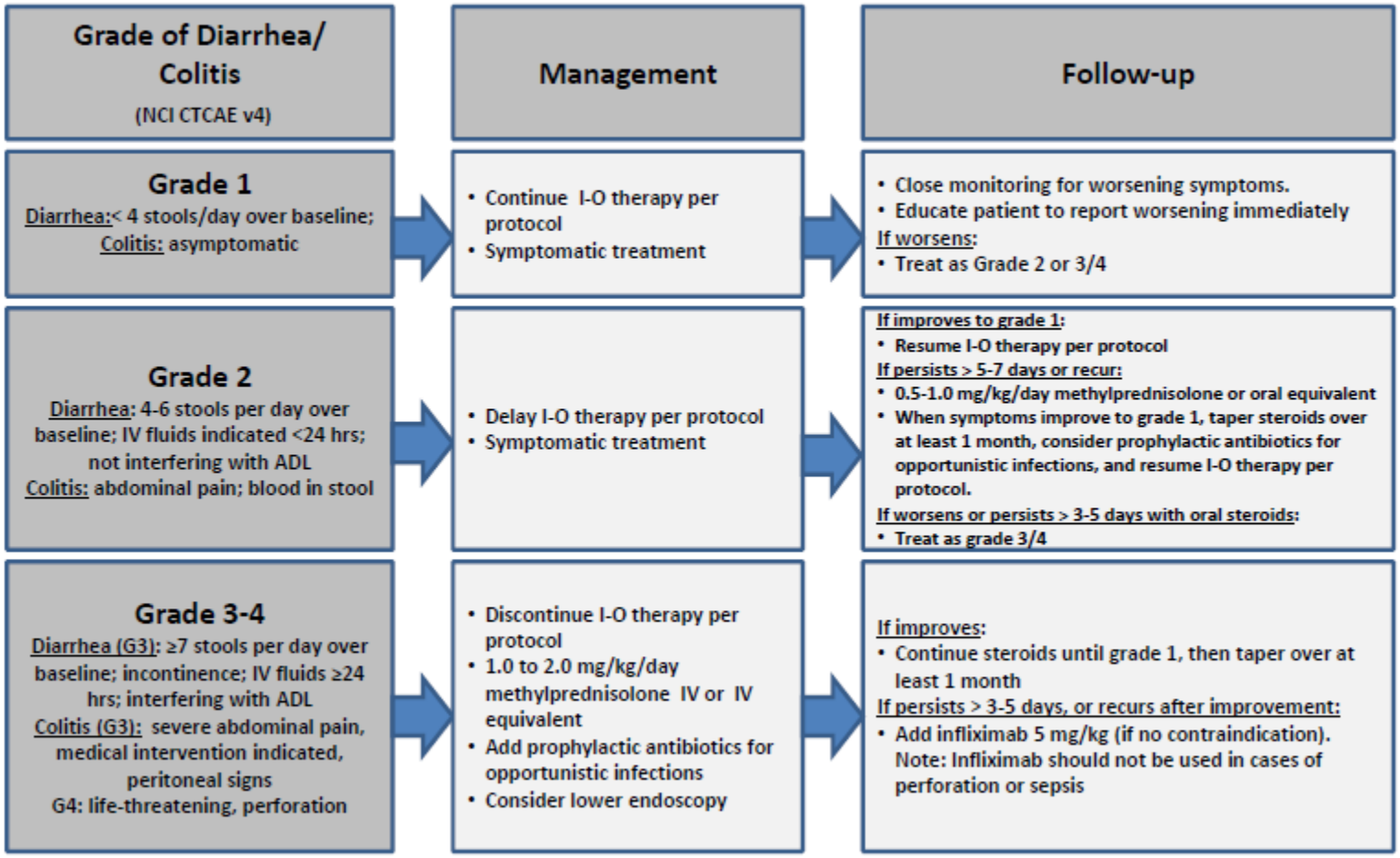
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

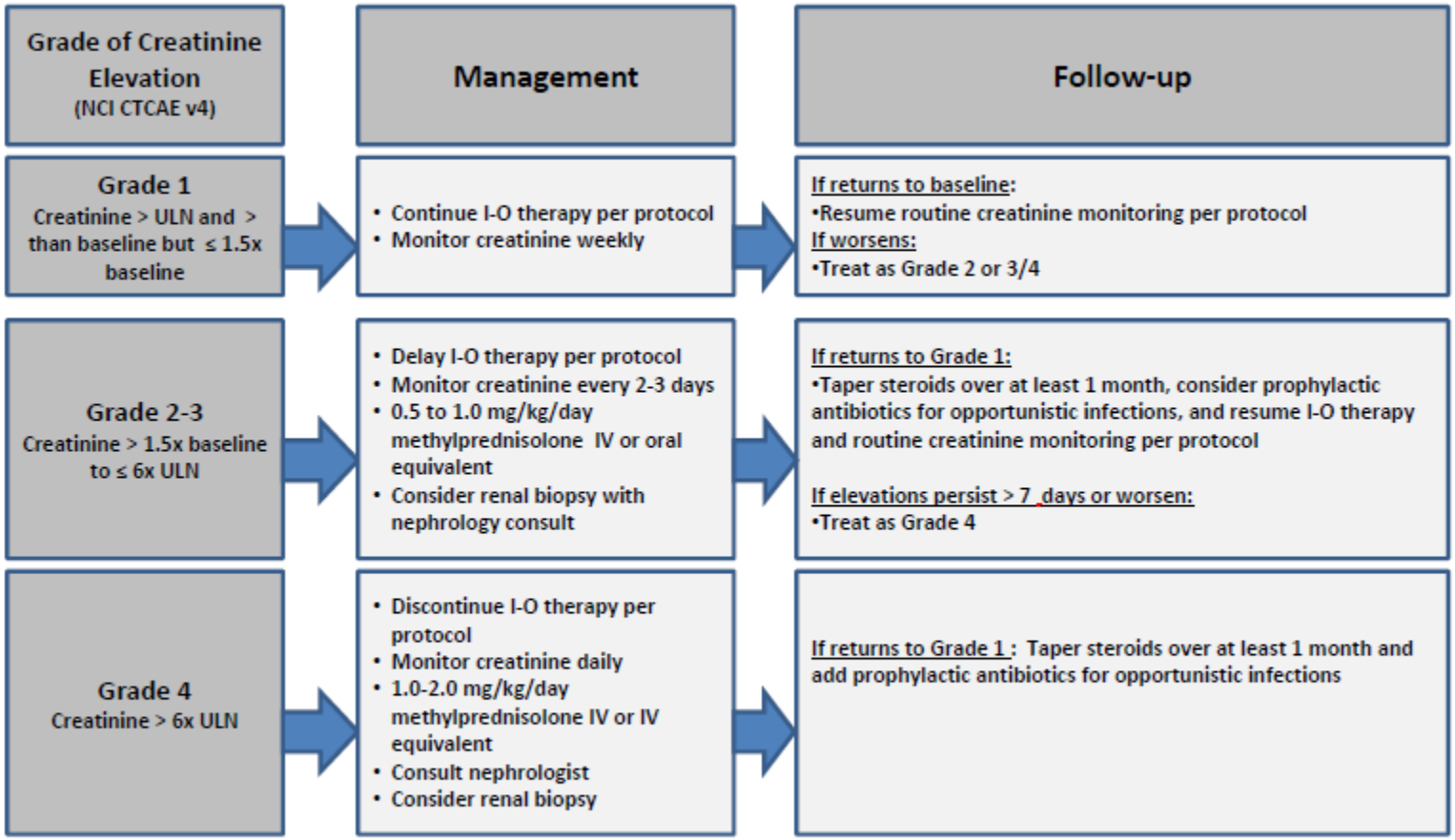


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

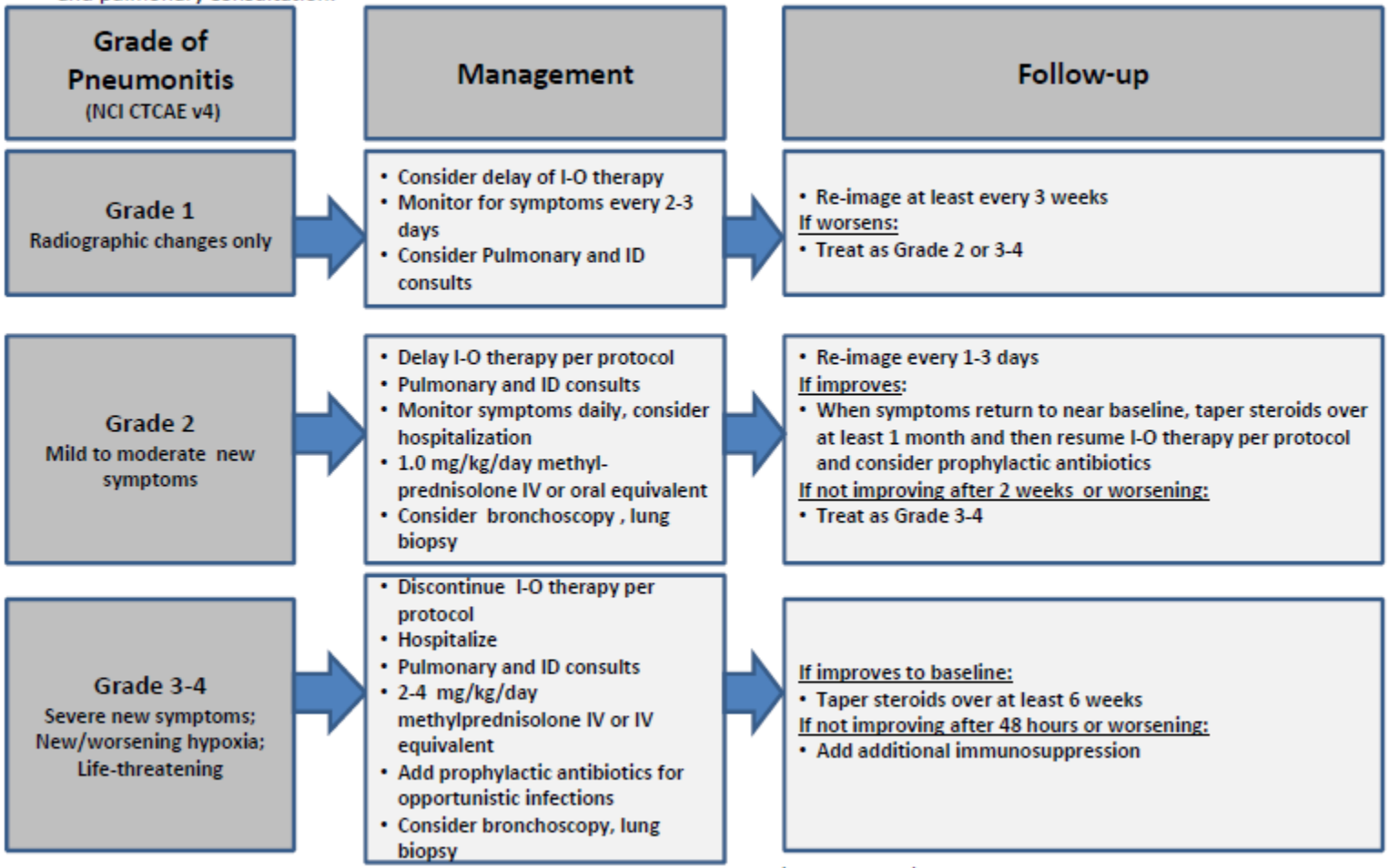


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

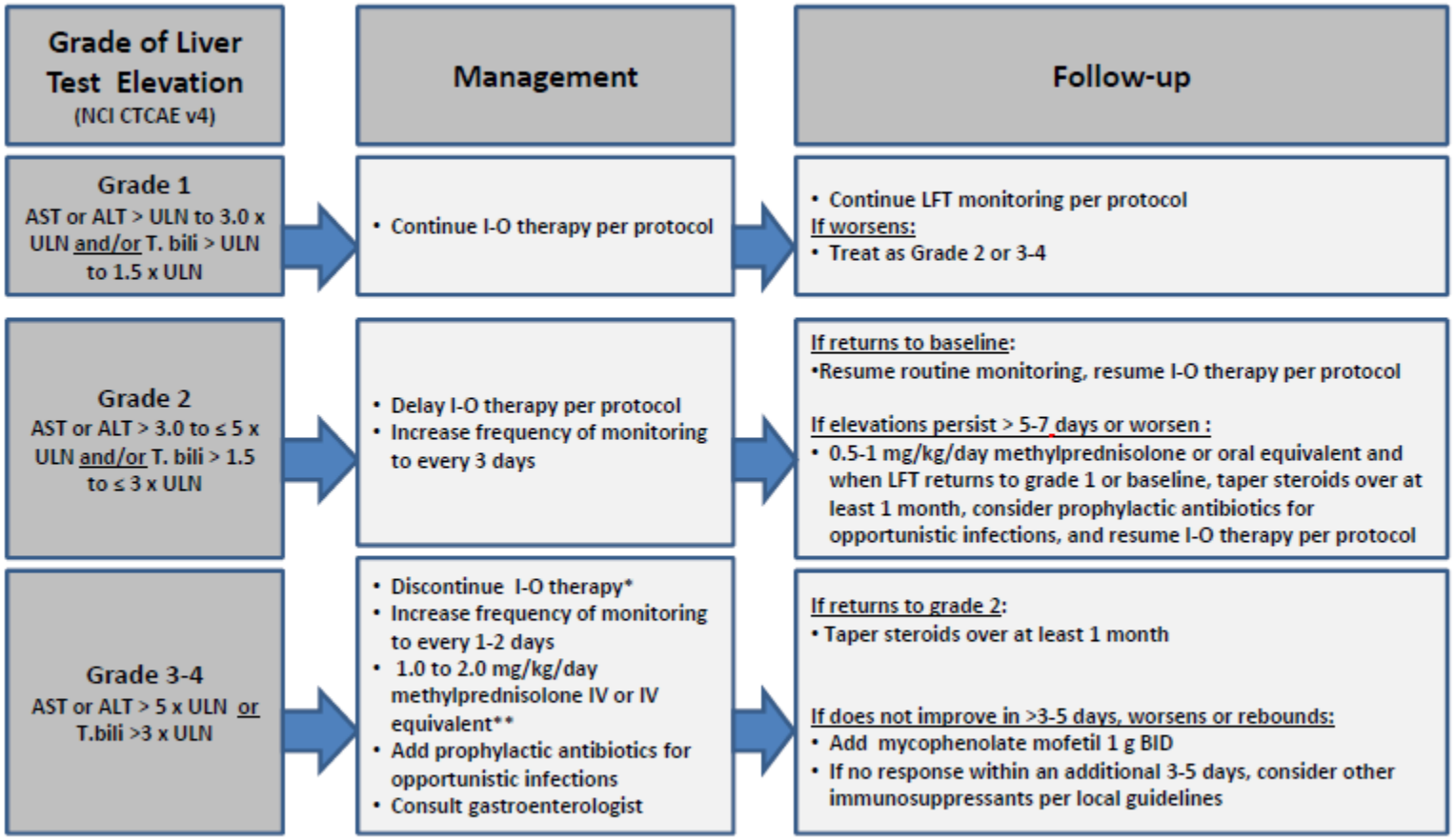


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

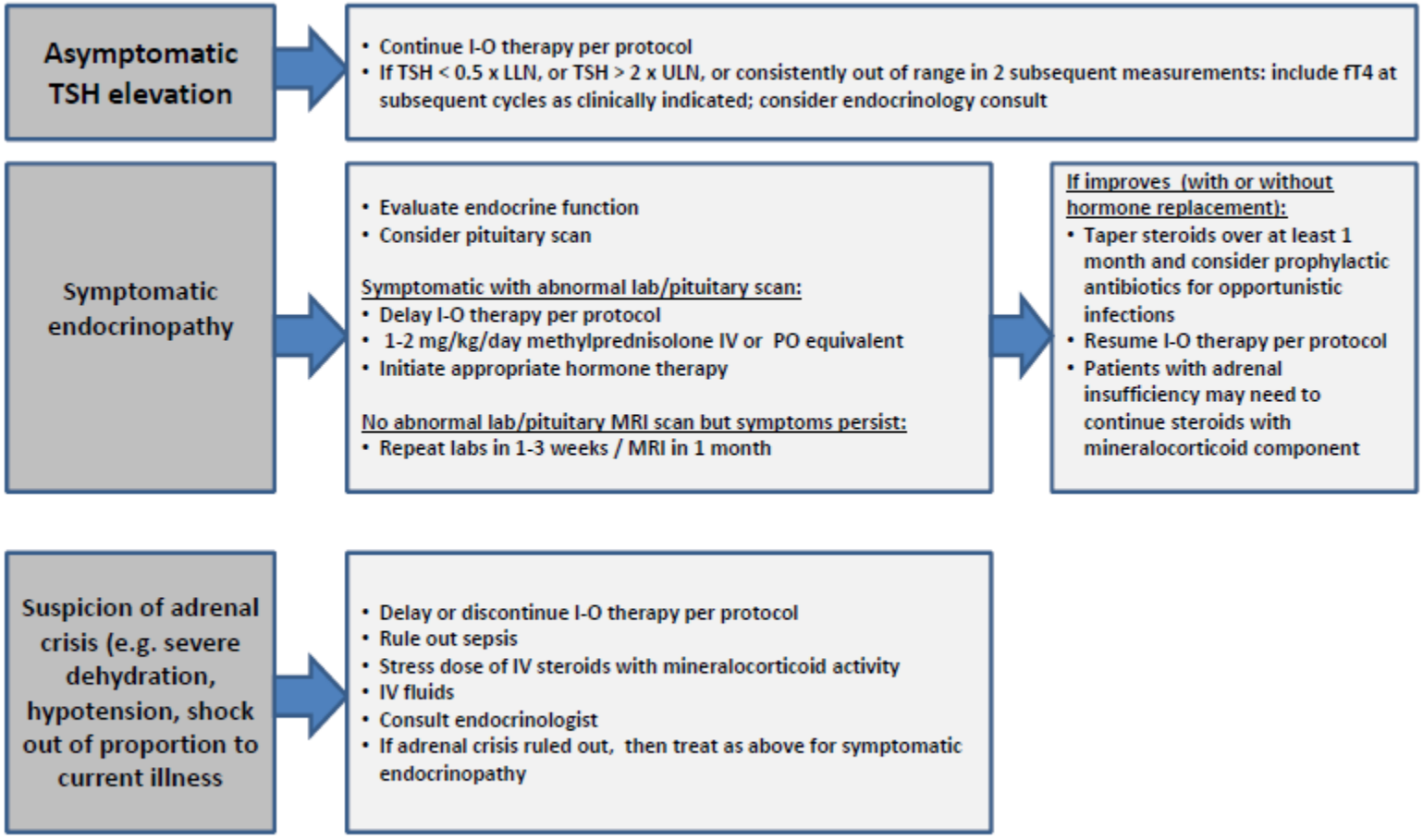
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

****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.

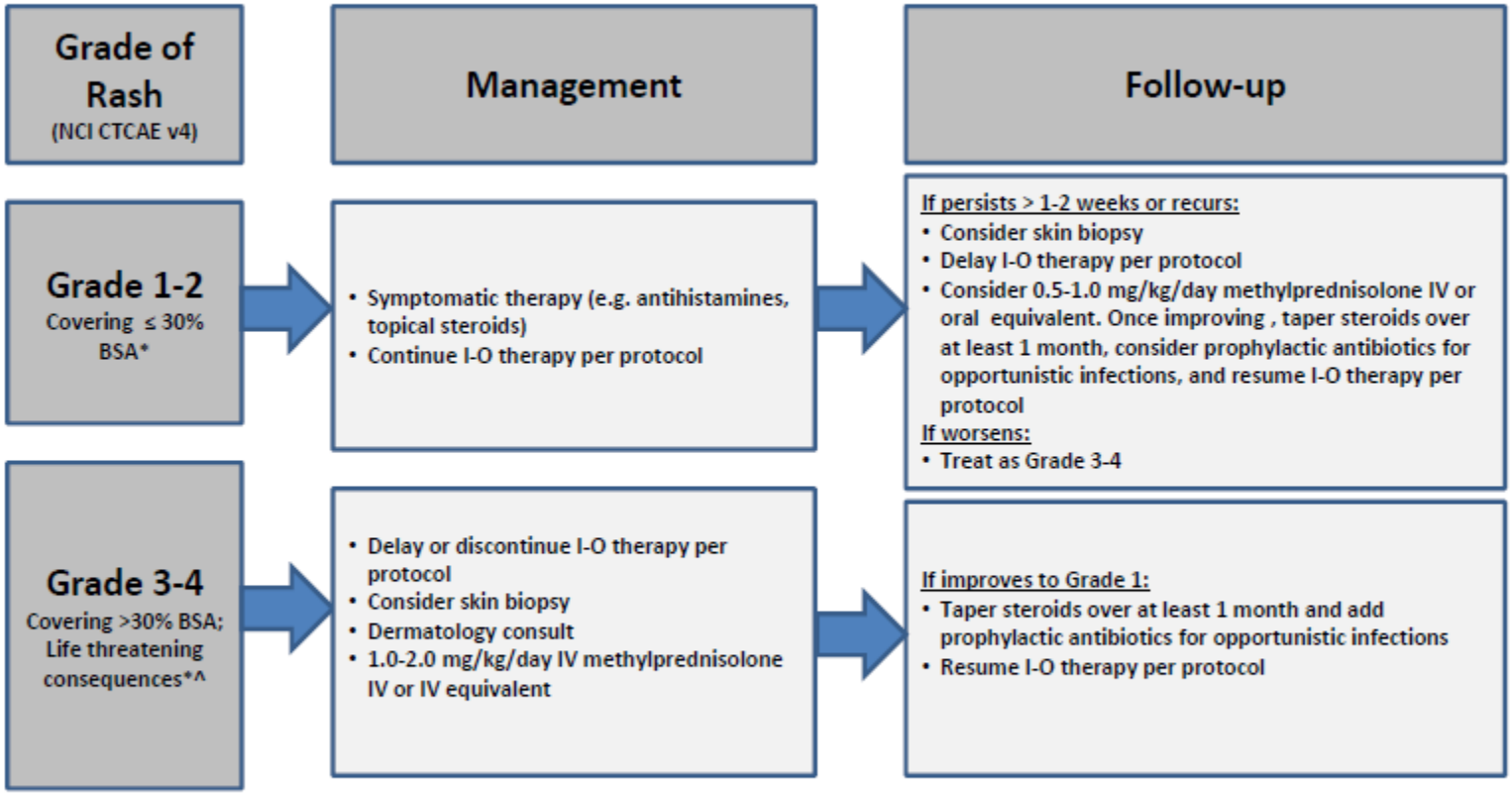


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

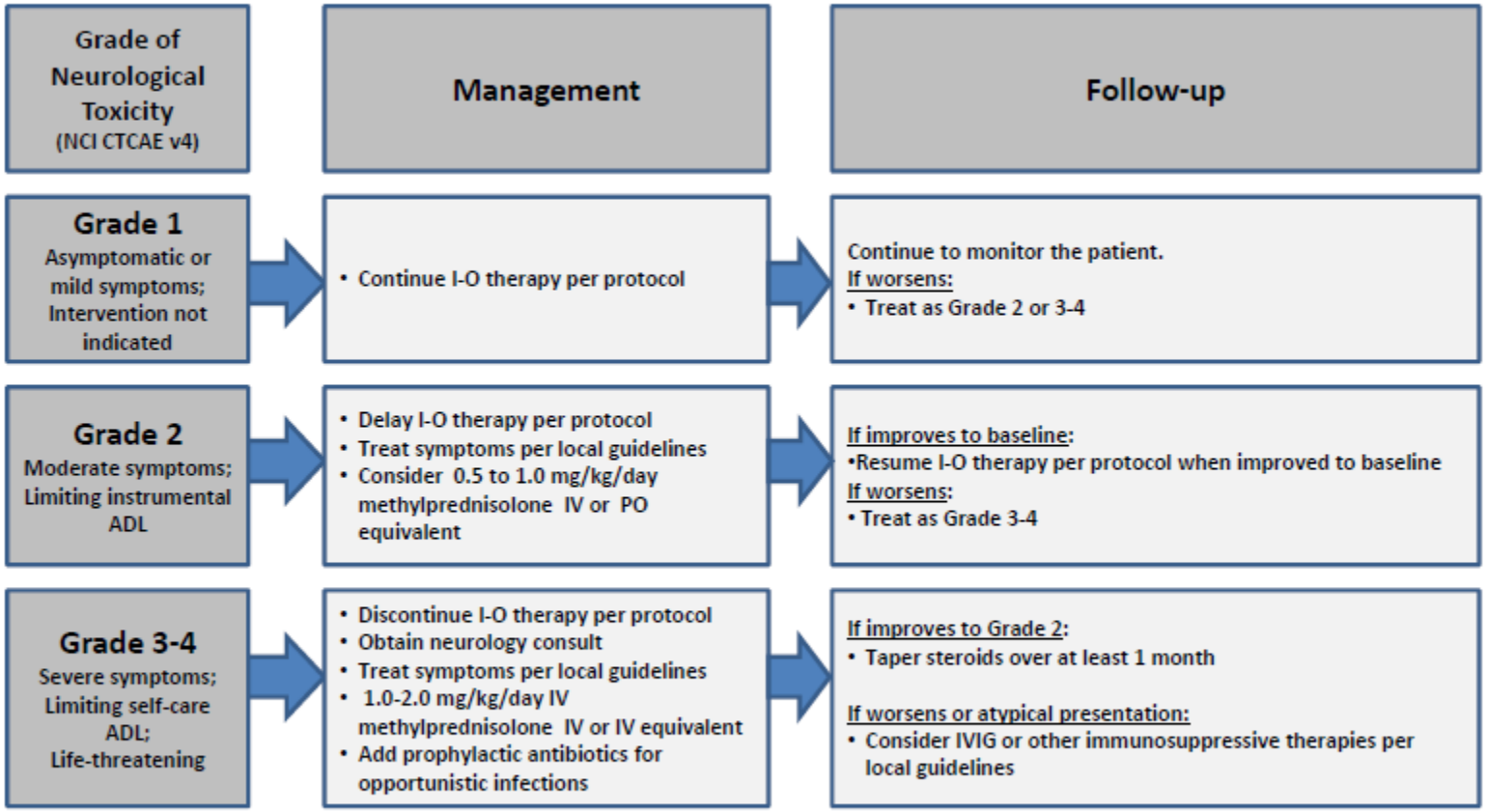


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Grade of Myocarditis (NCI CTCAE v4)	Management	Follow-up

Grade 2
Symptoms with mild to moderate activity or exertion
	• Delay I-O therapy; hospitalization with cardiac monitoring
	• Urgent cardiology consultation for evaluation and management
	  ○ Troponin and BNP
	  ○ ECG ± continuous cardiac monitoring
	  ○ Echocardiogram
	  ○ Cardiac MRI
	• Prompt initiation of 2 mg/kg/day methylprednisolone IV or equivalent
		• If worsens, intensify treatment according to grade
		• Upon recovery, taper steroids over at least 1 month with close monitoring of troponin and BNP as well as for new symptoms
		• Repeat cardiac MRI for post treatment assessment and cardiology follow-up
		• Retreatment may be considered after recovery and completion of steroid taper

Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated
 	
Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)
	• Permanently discontinue I-O therapy
	• Hospitalize to intensive cardiac monitoring
	• Cardiac evaluation to include:
	  – Troponin and BNP monitoring
	  – ECG ± continuous cardiac monitoring
	  – Echocardiogram
	  – Cardiac MRI
	  – Myocardial biopsy if feasible
	• Immediate initiation of 2 mg/kg/day methylprednisolone IV or 1 g IV bolus
	• Consider adding a second immunosuppressive agent
	Additionally, for Grade 4:
	• Hospitalize/transfer to institution with expertise in intensive cardiac monitoring
	• Consider ATG as second agent given its immediate effect
		• If no improvement, consider additional immunosuppression
		• Upon recovery, taper steroids over at least 1 month with close monitoring of troponin and BNP as well as for new symptoms
		• Repeat cardiac MRI for post treatment assessments and cardiology follow-up

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

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Approved v19.0 930038243 20.0